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C464 C584 C601 C612 C615 C62Y C620 C623 C624
C628 C633 C634 C635 C645 C65X C650 C652 C660
C662 C665 C670 C672 C675 C678 C694 C695 C697
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(56) Documents Cited
WO 96/22775 A WO 96/19773 A WO 96/02405 A

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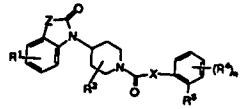
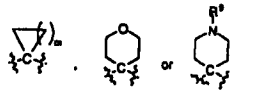
(54) Abstract Title
Tocolytic Oxytocin Receptor Antagonists

(57) This invention relates to certain novel benzoxazinone or quinolinone compounds and derivatives thereof, their synthesis, and their use as oxytocin receptor antagonists. One application of these compounds is in the treatment of preterm labor in mammals, especially humans. The ability of the compounds to relax uterine contractions in mammals also makes them useful for treating dysmenorrhea and stopping labor prior to cesarean delivery.

The compounds are of formulas.



wherein
Z is selected from CH_2O, CH=CH or CH_2CH_2;
X is selected from O, CH_2, CF_2,



R^1 is selected from hydrogen, halogen or C_{1-5} alkyl;
R^2 is selected from hydrogen, C_{1-5} alkyl, hydroxymethyl or $CONH_2$; and R_3 and R_4 are hydrogen or various organic substituents.

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TITLE OF THE INVENTION
TOCOLYTIC OXYTOCIN RECEPTOR ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS
Not Applicable

STATEMENT REGARDING FEDERALLY-SPONSORED R&D
Not Applicable

REFERENCE TO MICROFICHE APPENDIX
Not Applicable

FIELD OF THE INVENTION

The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture; such compounds are generally pharmacologically useful as agents in obstetric and gynecologic therapy in mammals. More specifically, the compounds of the present invention are useful in the treatment of preterm labor, dysmenorrhea and for stopping labor preparatory (i.e., prior) to cesarean delivery.

BACKGROUND OF THE INVENTION

In the field of obstetrics, one of the most important problems is the management of preterm labor. A significant number of the pregnancies progressing past 20 weeks of gestation experience premature labor and delivery, which is a leading cause of neonatal morbidity and mortality. Despite major advances in neonatal care, retention of the fetus *in utero* is preferred in most instances.

Tocolytic (uterine-relaxing) agents that are currently in use include β_2-adrenergic agonists, magnesium sulfate and ethanol. Ritodrine, the leading β_2-adrenergic agonist, causes a number of cardiovascular and metabolic side effects in the mother, including tachycardia, increased renin secretion, hyperglycemia (and reactive hypoglycemia in the infant). Other β_2-adrenergic agonists, including terbutaline and albuterol have side effects similar to those of ritodrine.

Magnesium sulfate at plasma concentrations above the therapeutic range of 4 to 8 mg/dL can cause inhibition of cardiac conduction and neuromuscular transmission, respiratory depression and cardiac arrest, thus making this agent unsuitable when renal function is impaired. Ethanol is as effective as ritodrine in preventing premature labor, but it does not produce a corresponding reduction in the incidence of fetal respiratory distress that administration of ritodrine does.

It has been proposed that an oxytocin antagonist would be the ideal tocolytic agent. In the last few years, evidence has accumulated to strongly suggest that the hormone oxytocin may be a physiological initiator of labor in several mammalian species including humans. Oxytocin is believed to exert this effect in part by directly contracting the uterine myometrium and in part by enhancing the synthesis and release of contractile prostaglandins from the uterine endometrium/decidua. These prostaglandins may, in addition, be important in the cervical ripening process. By these mechanisms, the process of labor (term and preterm) is initiated by a heightened sensitivity of the uterus to oxytocin, resulting in part as a result of a well-documented increase in the number of oxytocin receptors in this tissue. This "up-regulation" of oxytocin receptors and enhanced uterine sensitivity appears to be due to trophic effects of rising plasma levels of estrogen towards term. By blocking oxytocin, one would block both the direct (contractile) and indirect (enhanced prostaglandin synthesis) effects of oxytocin on the uterus. An oxytocin blocker, or antagonist, would likely be more efficacious for treating preterm labor than current regimens. In addition, since oxytocin at term has major effects only on the uterus, such an oxytocin antagonizing compound would be expected to have few, if any, side effects.

The compounds of the present invention are also useful in the treatment of dysmenorrhea. This condition is characterized by cyclic pain associated with menses during ovulatory cycles. The pain is thought to result from uterine contractions and ischemia, probably mediated by the effect of prostaglandins produced in the secretory endometrium. By blocking both the direct and indirect effects of oxytocin on the uterus, an oxytocin antagonist is more efficacious for treating

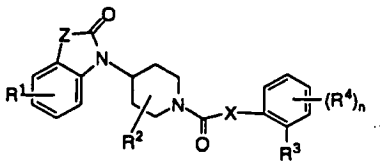
dysmenorrhea than current regimens. An additional use for the present invention is for the stoppage of labor preparatory to cesarean delivery.

It is, therefore, a purpose of this invention to provide substances which more effectively antagonize the function of oxytocin in disease states in animals, preferably mammals, especially in humans. It is another purpose of this invention to provide a method of antagonizing the functions of oxytocin in disease states in mammals. It is also a purpose of this invention to develop a method of preventing or treating the oxytocin-related disorders of preterm labor and dysmenorrhea by antagonizing the binding of oxytocin to its receptor.

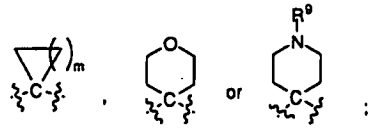
It has now been found that compounds of the present invention are antagonists of oxytocin and bind to the oxytocin receptor. When the oxytocin receptor is bound by the compounds of the present invention, oxytocin is antagonized by being blocked from its receptor and thus being unable to exert its biologic or pharmacologic effects. The compounds of the present invention are therefore useful in the treatment and prevention of oxytocin-related disorders of animals, preferably mammals and especially humans. These disorders are primarily preterm labor and dysmenorrhea. The compounds are also useful for stoppage of labor preparatory to cesarean delivery.

SUMMARY OF THE INVENTION

The compounds of the present invention are of the formula



wherein
Z is selected from CH_2O, CH=CH or CH_2CH_2;
X is selected from O, CH_2, CF_2,



R^1 is selected from hydrogen, halogen or C_{1-5} alkyl;

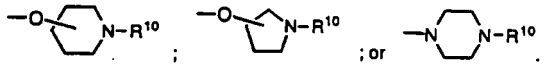
R^2 is selected from hydrogen, C_{1-5} alkyl, hydroxymethyl or $CONH_2$;

R^3 is selected from hydrogen; C_{1-5} alkoxy; mono- or polyhalogenated C_{1-5} alkoxy; substituted C_{1-5} alkoxy wherein the substituent on alkoxy is selected from carboxy, CO_2-C_{1-5} alkyl, $CONH_2$, pyridinyl or NH-R^5; unsubstituted or substituted phenyl wherein the phenyl is substituted with one to three substituents independently selected from C_{1-5} alkyl, halogen, CF_3 or CN; unsubstituted or substituted phenoxy wherein the phenoxy is substituted with one to three substituents independently selected from C_{1-5} alkyl, halogen, CF_3 or CN; unsubstituted or substituted pyrimidinyloxy wherein the substituent is CO_2NH_2; C_{1-5} alkyl; mono- or polyhalogenated C_{1-5} alkyl; hydroxy; C_{1-5} hydroxyalkyl; mono- or polyhalogenated C_{1-5} hydroxyalkyl; C_{1-5} alkenyl; mono- or polyhalogenated C_{1-5} alkenyl; C_{1-5} alkynyl; mono- or polyhalogenated C_{1-5} alkynyl; tetrahydrofuranyloxy; tetrahydrothiophenyloxy; C_{3-7} cycloalkyloxy; or

;

R^4 is selected from hydrogen; halogen; C_{1-5} alkyl; mono- or poly-halogenated C_{1-5} alkyl; C_{1-5} alkoxy; mono- or polyhalogenated

C_{1-5} alkoxy; substituted C_{1-5} alkoxy wherein the substituent on alkoxy is selected from carboxy, CO_2-C_{1-5} alkyl, $CON(R^8)_2$, $N(R^8)_2$ or morpolinyl; S-C_{1-5} alkyl; SO-C_{1-5} alkyl; SO_2-C_{1-5} alkyl; NHR^5; CN; carboxy; CO-C_{1-5} alkyl; $CON(R^8)_2$; pyridinyloxy; pyridinyloxy-N-oxide; triazolyl; tetrazolyl; morpholinyl; unsubstituted or substituted phenoxy wherein the phenoxy is substituted with one to three sub-stituents independently selected from C_{1-5} alkyl, halogen, CF_3 or CN;

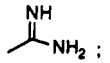


R^5 is selected from hydrogen, CO_2-C_{1-5} alkyl or $COCH_2$-Het;

each R^8 is independently selected from hydrogen or C_{1-5} alkyl;

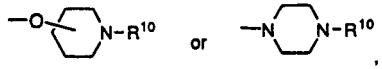
R^9 is selected from hydrogen, C_{1-5} alkyl, C_{3-6} cycloalkyl substituted C_{1-5} alkyl, CO_2-C_{1-5} alkyl or $COCH_2$-Het;

R^{10} is selected from hydrogen, C_{1-5} alkyl, C_{3-7} cycloalkyl substituted C_{1-5} alkyl, mono or polyhalogenated C_{1-5} alkyl, mono or polyhalogenated C_{1-5} alkyloxycarbonyl, hydroxy C_{1-5} alkyl, CO_2-C_{1-5} alkyl, $CON(R^8)_2$, CO-C_{1-5} alkyl, SO_2-C_{1-5} alkyl or

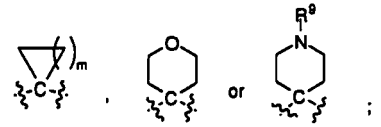


Het is selected from pyridinyl, imidazolyl and morpholinyl;
m is an integer from 1 to 5; and
n is an integer from 1 to 2;

provided that when Z is CH_2O or CH_2CH_2, and R^2 is hydrogen, C_{1-5} alkyl or $CONH_2$, and R^3 is hydrogen or C_{1-5} alkoxy, and R^4 is one or two of halogen, C_{1-5} alkoxy,



then X is selected from O, CF_2,



and the pharmaceutically acceptable salts thereof.

Illustrating the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. An example of the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. An illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

Further illustrating the invention is a method of eliciting an oxytocin antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above to elicit an oxytocin antagonizing effect.

An example of the invention are methods of treating preterm labor, preventing preterm labor, stopping preterm labor, stopping labor preparatory to cesarian delivery, and/or treating dysmenorrhea in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Further exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the

treatment of preterm labor, dysmenorrhea and/or stoppage of labor prior to cesarian delivery in a mammal in need thereof.

More particularly illustrating the invention is a drug which is useful for treating preterm labor, dysmenorrhea and/or stopping labor prior to cesarian delivery in a mammal in need thereof, the effective ingredient of the said drug being any of the compounds descibed above.

More specifically exemplifying the invention are methods of increasing fertility and embryonic survival in a farm animal in need thereof, and/or controlling the timing of estrus in a farm animal in need thereof, comprising administering to the farm animal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Another example of the invention is a method for improving survival of a farm animal neonate comprising controlling timing of parturition to effect delivery of the neonate during daylight hours by administering to a farm animal which is expected to deliver the neonate within 24 hours a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Additional illustrations of the instant invention are methods of antagonizing vasopressin from binding to its receptor site, inducing vasodilation, treating hypertension, inducing diuresis and/or inhibiting platelet agglutination in a mammal in need thereof comprising the step of administering to the mammal a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

BRIEF DESCRIPTION OF THE DRAWINGS

Not Applicable

DETAILED DESCRIPTION OF THE INVENTION

Representative compounds of the present invention are oxytocin antagonists which display submicromolar affinity for the human oxytocin receptor. Compounds of this invention were found to have IC_{50} values for the human oxytocin receptor in the range of 0.1- 100 nM.

The compounds of the present invention are administered in dosages effective to antagonize the oxytocin receptor where such treatment is needed, as in the treatment of preterm labor. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following:

Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isothionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide and Valerate.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The compounds of the present invention, may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which is not specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, etc.).

The term "alkoxy," as used herein, refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C_{1-5} alkoxy), or any number within this range (i.e., methoxy, ethoxy, etc.).

The term "halogen" shall include iodine, bromine, chlorine and fluorine.

The terms "mono- or polyhalogenated C_{1-5} alkyl," "mono- or polyhalogenated C_{1-5} alkoxy," "mono- or polyhalogenated C_{1-5} alkenyl," "mono- or polyhalogenated C_{1-5} alkynyl" and "mono- or polyhalogenated C_{1-5} hydroxyalkyl," as used herein, include both straight and branched chain C_{1-5} alkanes, alkoxides, alkenes, alkynes or hydroxyalkanes wherein one or more of the hydrogen atoms on the alkyl, alkoxy, alkenyl, alkynyl or hydroxyalkyl chain is replaced with a halogen atom (e.g., CF_3, OCH_2CF_3).

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substitutent.

Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

The term "preterm labor" shall mean expulsion from the uterus of a viable infant before the normal end of gestation, or more particularly, onset of labor with effacement and dilation of the cervix before the 37th week of gestation. It may or may not be associated with vaginal bleeding or rupture of the membranes.

The term "dysmenorrhea" shall mean painful menstruation.

The term "cesarean delivery" shall mean incision through the abdominal and uterine walls for delivery of a fetus.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The ability of the compounds of the present invention to antagonize oxytocin makes these compounds useful as pharmacologic agents for mammals, especially for humans, for the treatment and prevention of disorders wherein oxytocin may be involved. Examples of such disorders include preterm labor and dysmenorrhea. These compounds may also find usefulness for stoppage of labor preparatory to

cesarean delivery. Additionally, such compounds are useful in inducing contraception in mammals inasmuch as oxytocin antagonists have now been shown to inhibit the release of oxytocin-stimulated luteinizing hormone (LH) by anterior pituitary cells.

The present invention is also directed to combinations of the compounds of the present invention with one or more agents useful in the treatment of disorders such as preterm labor, dysmenorrhea and stopping labor prior to cesarean delivery. More specifically, the compounds of the instant invention may be effectively administered in combination with effective amounts of other tocolytic agents used in the treatment of preterm labor such as β-adrenergic agonists (e.g., ritodrine, isoproterenol, terbutaline, albuterol), magnesium sulfate, ethanol, other oxytocin antagonists (e.g., atosiban), calcium transport blockers (e.g., nicardipine, nifedipine), prostaglandin synthesis inhibitors (e.g., indomethacin), nitric oxide donors (e.g., nitroglycerine, S-nitroso-N-acetylpenicillamine), phosphodiesterase inhibitors, and progestins (e.g., progesterone). Preferred combinations are simultaneous or alternating treatments of an oxytocin receptor antagonist of the present invention and a second tocolytic agent. In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. The compounds of the instant invention may also be used in combination with antenatal steroids (e.g., dexamethasone). This particular combination has beneficial effects on the neonate by both decreasing uterine activity to prolong gestation and increasing fetal maturation. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating oxytocin related conditions includes in principle any combination with any pharmaceutical composition useful for treating preterm labor, dysmenorrhea or stopping labor prior to cesarean delivery.

The oxytocin antagonist compounds of the present invention are also useful for improving reproductive efficiency in farm animals. In certain farm animals (e.g., sheep, cattle, swine, horses and goats), the beginning of the estrous cycle is typically marked by behavioral estrus when the female animal accepts the male for mating. Ovulation of the ovarian follicle occurs shortly after onset of estrus and cells in the follicle give rise to the corpus luteum. The cells that form the corpus luteum produce progesterone and they also produce oxytocin. The secretion of oxytocin from the corpus luteum and/or pituitary acts on the uterine endometrium to stimulate the secretion of prostaglandins (in particular PGF) which, in turn, causes the regression of the corpus luteum of the ovary. PGF is, therefore, the luteolytic hormone. In the cycling animal (i.e., where mating and fertilization have not occurred), destruction of the corpus luteum removes the source of progesterone which is key to the preparation of the uterus for pregnancy. The presence of a viable conceptus (i.e., the embryo and its associated membranes) is necessary to prevent the luteolytic process. In fact, the first key signal that the conceptus must produce is the one to prevent regression of the corpus luteum (i.e., the maternal recognition of pregnancy signal). Thus, in the animal where mating and fertilization have occurred, the conceptus secretes a factor that antagonizes the action of oxytocin to induce luteolysis. This results in maintenance of a functioning corpus luteum and the continued secretion of progesterone which is obligatory to the initiation of pregnancy.

Administration of an oxytocin antagonist of the present invention at this critical period after fertilization (i.e., just prior to or during the period of maternal recognition of pregnancy) supplements the natural signal from the conceptus (i.e., maternal recognition of pregnancy) to prolong corpus luteal function. The result is to increase pregnancy rates by enhancing the chances of impregnation through a reduction in embryonic loss. Thus, to improve fertility and embryonic survival in a farm animal, a mated animal, for example, a mated ewe, is treated with an oxytocin antagonist compound beginning on between day 10 to day 15 after onset of estrus. The oxytocin antagonist compound is administered to the mated animal for a period of one day to three

weeks, preferably one week to three weeks, most preferably one week to two weeks.

The compounds of the present invention are also useful for controlling the timing of parturition in farm animals so that delivery of the neonates occurs during the daytime. Approximately 80% of livestock are delivered at night and up to 5 to 10% of newborns die because the deliveries are not monitored properly. An oxytocin antagonist compound of the present invention administered to the mother on the evening before expected delivery delays parturition so that the delivery occurs during the daylight hours. By delaying the timing of parturition, proper monitoring of the delivery and the neonates is ensured, resulting in increased survival rates of the newborns.

In addition, the oxytocin antagonists of the instant invention can also be used to control the timing of estrus in a cycling farm animal by preventing luteal regression. An oxytocin antagonist compound of the instant invention is administered to a cycling farm animal prior to expected estrus to prevent regression of the corpus luteum. Daily administration of the compound retards estrus until administration of the compound ceases. Preferably, the oxytocin antagonist compound is administered at least 1 day prior to expected estrus. By delaying estrus in a group of farm animals, a farmer can synchronize estrus among the group to provide time and cost savings in farm management.

The compounds of the present invention also bind to the vasopressin receptor and are therefore useful as vasopressin antagonists. Vasopressin antagonists are useful in the treatment or prevention of disease states involving vasopressin disorders; thus, the compounds are useful for inducing vasodilation, treating hypertension, inducing diuresis, inhibiting platelet agglutination and treating congestive heart failure.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous

(both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a tocolytic agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.0025 to 5.0 gm/day orally. More particularly, when administered orally for the treatment of preterm labor, an effective daily dose will be in the range of 0.005 mg/kg to about 100 mg/kg of body weight, preferably, from 0.01mg/kg to 50 mg/kg, most preferably from 0.1 mg/kg to 50 mg/kg, administered in single or divided dose. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from 0.1 to about 10 mg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage

administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, zanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethyl-aspartamidephenol, or polyethyleneoxidepolylysine

substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

AIBN = azo bis(isobutyronitrile)
Bn = benzyl
Boc = t-butyloxycarbonyl
BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
DCC = 1,3-dicyclohexylcarbodiimide
DCM = dichloromethane
DEAD = diethyl azodicarboxylate
DIEA = diisopropylethylamine
DMAP = 4-dimethylaminopyridine
DME = dimethoxyethane
DMF = dimethylformamide
DMSO = dimethyl sulfoxide
Et = ethyl
EtOAc = ethyl acetate
EtOH = ethanol
EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
FAB MS = fast atom bombardment mass spectroscopy
HOAc = acetic acid
HOBT or HBT = 1-hydroxybenzotriazole
HPLC = high performance liquid chromatography
IPA = isopropyl acetate
LAH = lithium aluminum hydride
LDA = lithium diisopropylamide
m-CPBA or MCPBA = meta-chloroperoxybenzoic acid
Me = methyl

MeOH = methanol
MOM = methoxymethyl
MTBE = methyl tert-butyl ether
NBS = N-bromosuccinimide
NCS = N-chlorosuccinimide
NMR = nuclear magnetic resonance
Ph = phenyl
PPTS = pyridinium p-toluenesulfonate
t-Bu = tert-butyl
TBAF = tetrabutylammonium fluoride
TEA = triethylamine
Tf = triflate = SO_2CF_3
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = thin layer chromatography
TMEDA = N, N, N', N'-tetramethylethylenediamine
TMS = trimethylsilyl
TMS-allyl = allyltrimethylsilane

The compounds of the present invention can be prepared readily according to the following Flowsheet diagrams and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

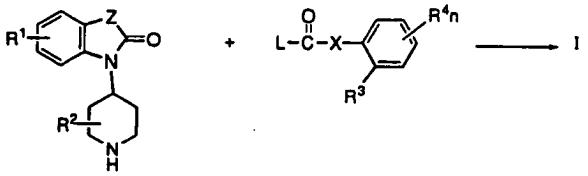
Representative compounds of the invention are any or all of those specifically set forth in the following Examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

The general procedure for making the compounds claimed in this invention can be readily understood and appreciated by one skilled in the art from viewing the following Flowsheet schemes.

Flowsheet 1 illustrates the basic condensation reaction from which all of the claimed compounds can be prepared. As shown, Structure A can be reacted with Structure B in the presence of a suitable solvent and reagent combination to effect the condensation reaction to form the Structure I, which is the generic description of the claimed compounds in this invention.

The variables R^1, R^2, R^3, $R^4{}_n$, X and Z are as defined in the Summary of the Invention, and Claim 1, with the exception of "L", which is representative of a leaving group, e.g., halogen, benzotriazolyloxy and the like. When L is e.g., chloro, a suitable basic reagent such as pyridine or triethylamine can be used to neutralize the formed hydrogen chloride. When a carboxylic acid is used, where L is hydroxy, EDC and HOBT can be used to combine with the liberated water in the reaction. In light of these examples, other conventional procedures will become obvious to one skilled in the art for carrying out the condensation to make the novel compounds of Structure I.

FLOWSHEET 1



A

B

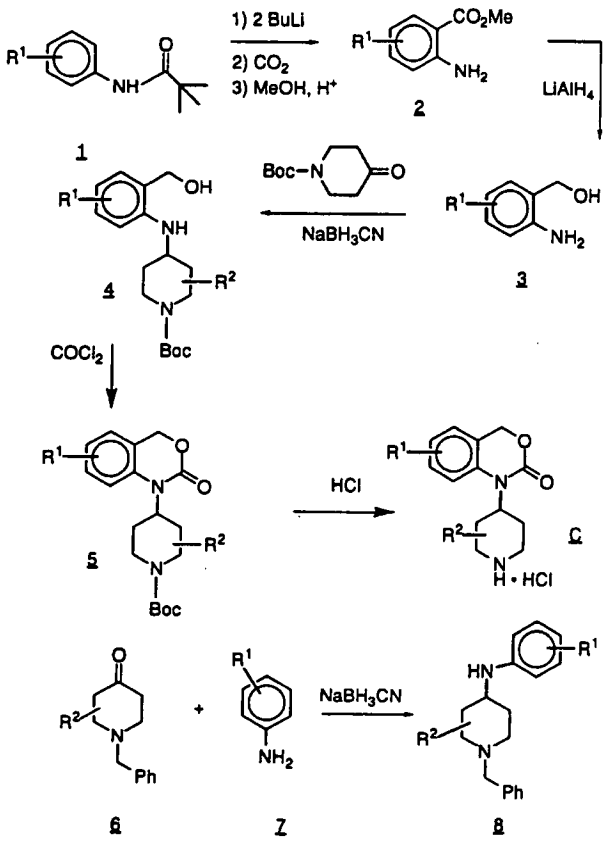
Flowsheet 2 describes synthetic routes to make the starting intermediates, benzoxazinone C and the dihydroquinoline D.

As illustrated in the synthesis of C, an aniline 1, protected with an N-t-butoxycarbonyl group (Boc), can be reacted with butyllithium and carbon dioxide, followed by treatment with acidic methanol to yield a methyl anthranilate 2, which can be subsequently reduced to the hydroxymethyl analog 3 by treatment with a reducing agent, e.g., lithium aluminium hydride, which product can then be reacted with N-Boc-4-piperidone in the presence of $NaBH_3CN$ to form a 2-hydroxymethyl-N-piperidinyl derivative 4 which can then be reacted with phosgene to form an N-piperidinylbenzoxazinone 5, which can be subsequently treated with e.g., HCl to remove the Boc protecting group to form the starting benzoxazinone intermediate C.

As illustrated in the synthesis of D, a benzyl-protected 4-piperidone 6 can be reacted with an aniline 7 in the presence of $NaBH_3CN$ to form an N-piperidinyl substituted aniline 8, which can be reacted with 3-ethoxyacryloyl chloride to yield the condensation product 9, which can be ring closed with sulfuric acid to yield the N-protected quinolinone 10, which can then be treated with hydrogen atmosphere over a palladium on carbon catalyst to yield the starting dihydroquinolinone of A in Flowsheet 1 to produce generic compounds of Structure I.

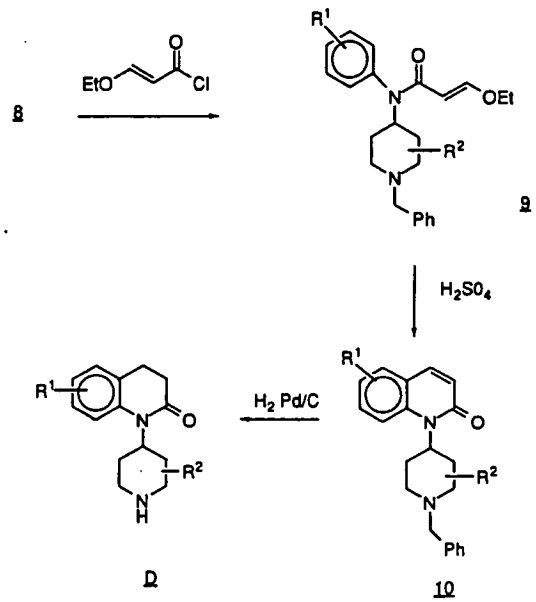
Either subgeneric Structures C or D can be used as Structure A in Flowsheet 1 to produce subgeneric compounds of Structure I.

FLOWSHEET 2



1 2 3 4 5 6 7 8

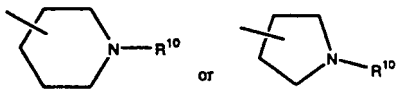
FLOWSHEET 2 CONT'D.



8 9 10 D

Flowsheet 3 describes two syntheses of subgeneric Structure E, which can be used as Structure B in the general scheme in Flowsheet 1 to produce subgeneric compounds of Structure I.

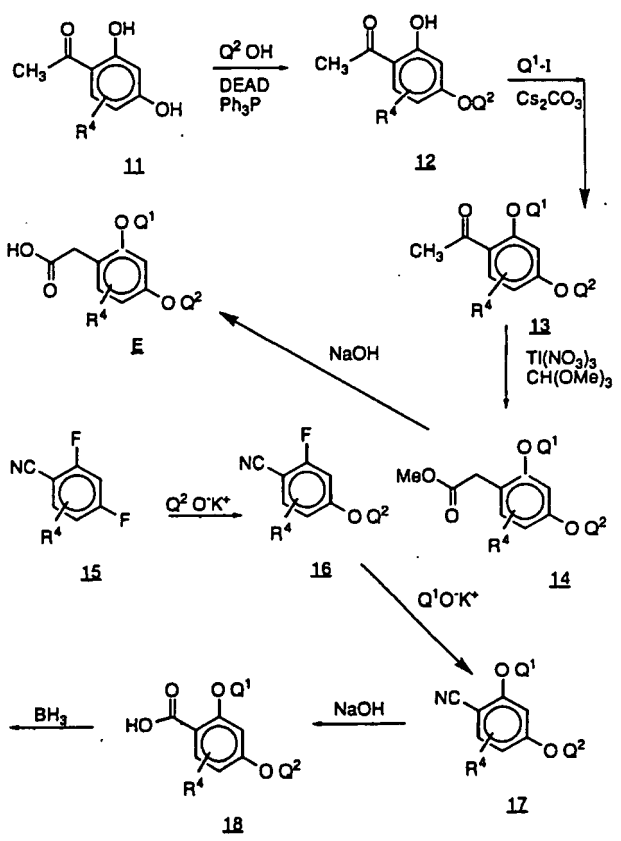
As illustrated, the acetyl hydroquinone 11, can be selectively etherified by reacting with the hydroxy compound, Q^2OH, where Q^2 is:



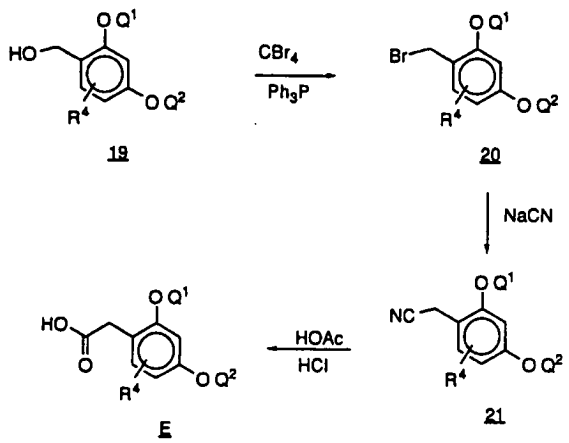
and wherein the etherification can be carried out in the presence of an azodicarboxylate, e.g., DEAD, and triphenylphosphine to form an ether 12, which can then be further etherified by reaction with a halide, Q^1Hal, or $Q^1OSO_2CF_3$, where Hal is halide being chloro, bromo or iodo, and Q^1 is C_{1-5}alkyl, mono- or polyhalogenated C_{1-5}alkyl, or substituted C_{1-5}alkyl wherein the alkyl can be substituted with carboxy, CO_2-C_{1-5}alkyl, $CONH_2$, pyridinyl or NHR^5; wherein R^5 is defined in the Summary of the Invention and Claim 1. The diether 13 can be further treated with e.g., thallium nitrate and trimethoxymethane to form a methoxycarbonylmethyl derivative 14, which can be treated with a basic reagent, e.g., sodium hydroxide, to form the carboxylic acid starting material E.

In an alternate synthesis of E, the difluorocyanobenzene compound 15 can be sequentially treated with the reagent Q^2OK and then with the reagent Q^1OK to form the diether 17, which can then be treated with a basic reagent, e.g., sodium hydroxide, to form the carboxylic acid 18, which can then be reduced with BH_3 to yield alcohol 19, which can be converted to the bromo compound 20 by reaction with triphenylphosphine and tetrabromomethane, which can then be reacted with a cyanide salt to yield the cyanomethyl derivative 21, which can then be hydrolyzed to the carboxylic acid and starting material E.

FLOWSHEET 3



FLOWSHEET 3 CONT'D.

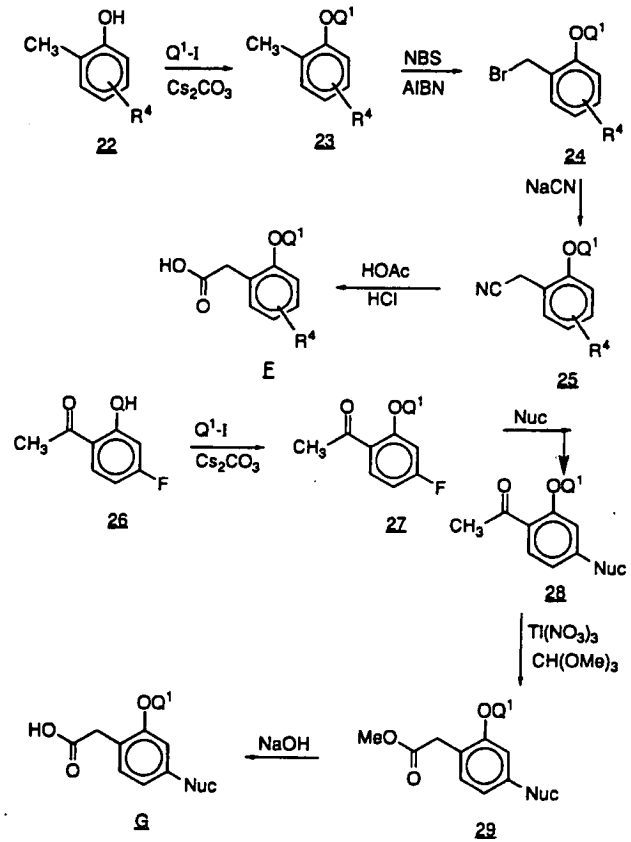


Flowsheet 4 describes the synthesis of intermediates F and G.

As illustrated, a synthesis of F can be carried out by starting with the phenol 22, which can be etherified with Q^1I (or $Q^2OSO_2CF_3$) to form the ether 23, then brominated with N-bromosuccinimide, the product of which is then treated with sodium cyanide to form the cyano compound 25, which is then hydrolyzed to the carboxylic acid of intermediate compound F.

The synthesis of G follows a similar pattern wherein the starting phenol 26 is etherified with Q^1I (or $Q^2OSO_2CF_3$) to form the ether 27, which is then treated with a nucleophilic containing compound, e.g., mercaptide salt, alkoxide salt or amine, to form 28, which then undergoes the conversion to the methoxycarbonylmethyl compound 29, which is then hydrolyzed to the carboxylic acid G.

FLOWSHEET 4

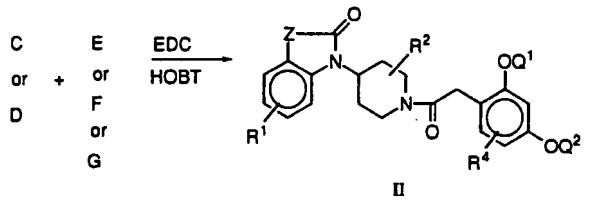


Flowsheet 5 describes the general synthesis of compounds of Structure II, being a subgenus of Structure I in which either C or D intermediates can be reacted with intermediates E, F or G, to produce Structure II compounds in which the R4 substituents are fluoro or C_{1-5}alkoxy groups.

Also illustrated are other transformations which can be effected involving Structure III, a subgenus of Structure II where R^3 is trifluoroethoxy and R4 is N-Boc substituted piperidinyloxy.

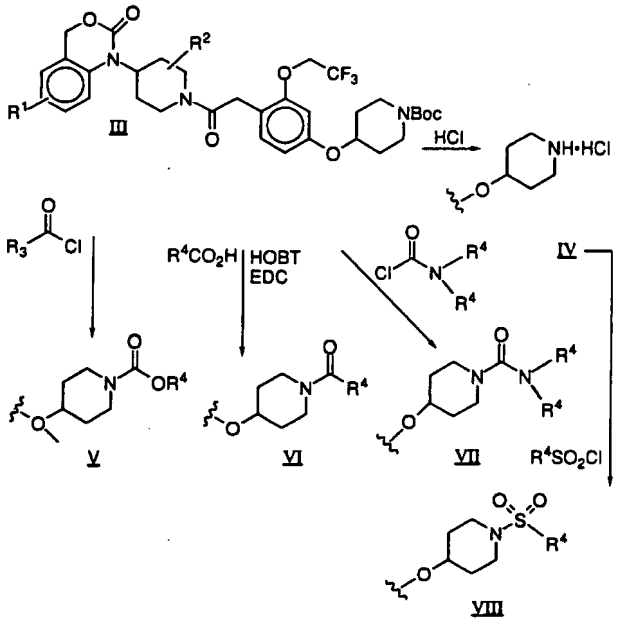
As seen, the Boc protecting group can be removed with acid hydrolysis to yield the secondary amine IV, which can be preferentially reacted with $Q^3O(CO)Cl$, where Q^3 is C_{1-5}alkyl or mono- or polyhalogenated C_{1-5}alkyl, to yield the intermediate V; IV can also be reacted with Q^3CO_2H to yield VI; IV can also be treated with $N(Q^4)_2(CO)Cl$, where Q^4 is H, C_{1-5}alkyl, to yield intermediate VII; IV can also be further treated with Q^3SO_2Cl to yield the intermediate VIII; also IV can be reacted with an aldehyde Q^5CHO, where Q^5 is C_{1-4}alkyl, mono or polyhalogenated C_{1-4}alkyl, C_{3-7} cycloalkyl substituted C_{1-4}alkyl, in the presence of $NaBH_3CN$ to yield intermediate IX; the starting IV can also be further treated with a ketone, $Q^6Q^7(CO)$, where Q6 and Q7 are independently selected from C_{1-2}alkyl, mono- or polyhalogenated C_{1-2}alkyl, or C_{3-7} cycloalkyl substituted C_{1-2}alkyl, with the proviso that the total number of carbons in the group representing R^{10} is 5, to yield the intermediate X; the starting IV can also be reacted with an epoxide $Q^6Q^7CH(CH_2)O$, where Q^6, Q^7 are defined above, to yield the intermediate XI, with the proviso that the total number of carbons in the group representing R^{10} is 5.

FLOWSHEET 5



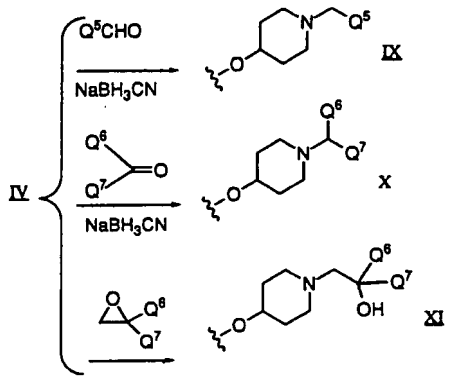
II

Examples of other tranformations



5

FLOWSHEET 5 CONT'D.



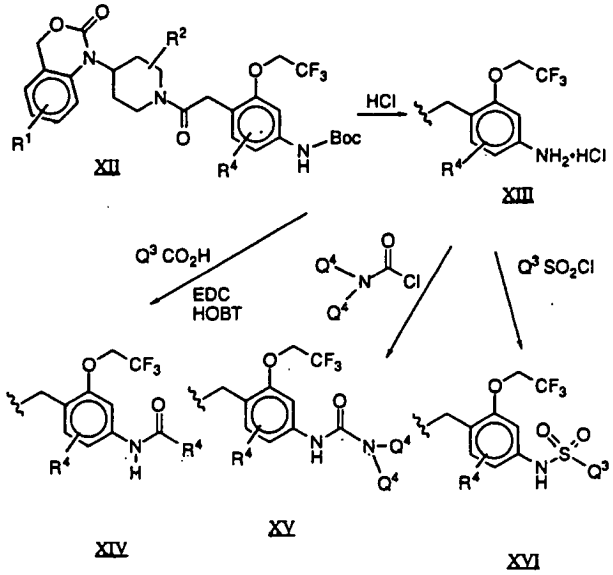
Flowsheet 6 illustrates transformations which can be carried out with Structure XII, which a subgenus of Structure I wherein R^4 is Boc protected amine.

As seen, XII can be deprotected to the amine, XIII; the intermediate XIII can be treated with with a carboxylic acid to yield XIV; XIII can also be reacted with a carbamoyl chloride to yield a urea XV; and, also XIII can be treated with a sulfonyl chloride to yield a sulfonamide XVI.

Further, the intermediate of Structure XVII, can be reacted with a variety of reagents to produce derivatives of the 4-hydroxy group.

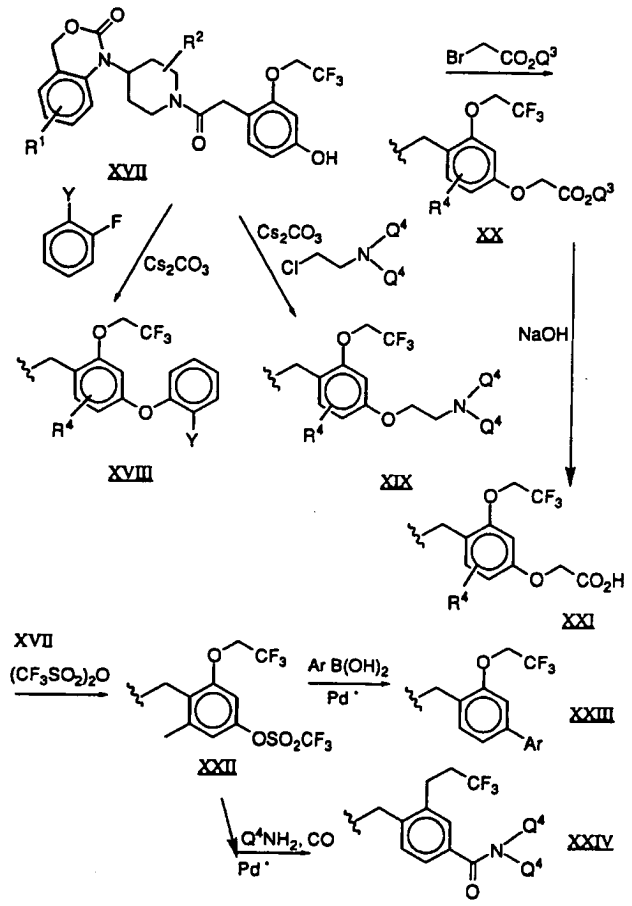
As seen, XVII can be reacted with a bromoacetate to yield the diether XX, which can be treated with caustic to yield the carboxylic acid XXI; XVII can also be reacted with an aminoalkylchloride to yield the aminoalkylether derivative XIV; further, XVII can be reacted with an ortho-substituted fluorobenzene, where Y is $C_{1\text{-}5}$alkyl, halogen, trifluoromethyl or cyano to yield diether XVIII; additionally, XVII can be reacted with trifluoromethylsulfonic anhydride to yield the sulfonyl derivative XXII; XXII can in turn be reacted with a dihydroxyboronaryl compound where Ar is phenyl, which can be substituted with by Y, defined above, to yield the aromatic substituted compound XXIII; also, XXII can be treated with an amine, CO over a palladium catalyst to yield the amide XXIV.

FLOWSHEET 6



XII XIII XIV XV XVI

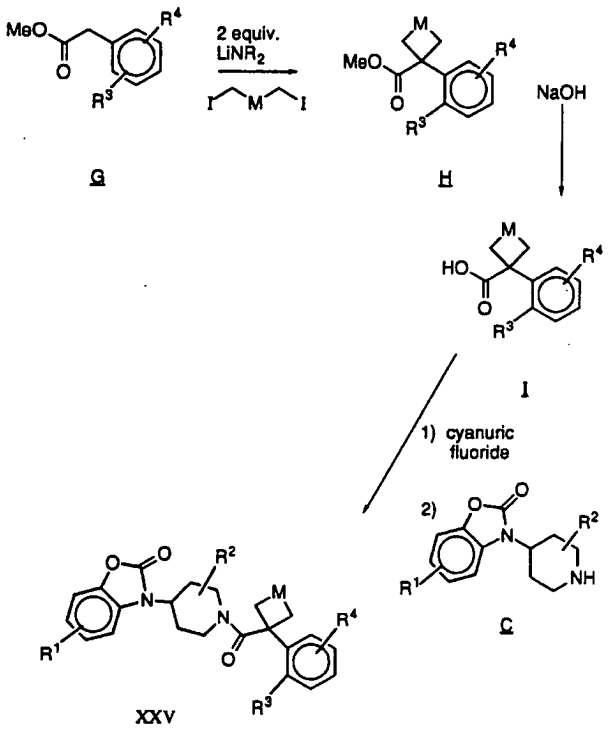
FLOWSHEET 6 CONT'D.



Flowsheet 7 illustrates the process of inserting a cyclic alkyl group for X in the Structure I.

As seen, intermediate G can be reacted with the reagent I-CH_2-M-CH_2-I, where M is selected from the group consisting of: $(CH_2)_m$ where m is 1-5 carbons; -(CH_2-O-CH_2)- ; and -(CH_2-NR^9-CH_2)-, where R9 is defined in Claim 1 and the Summary of the Invention. The product H can be treated with caustic to form the carboxylic acid J which can then be reacted with the intermediate C, from Flowsheet 2 to yield the product XXV.

FLOWSHEET 7



In the Examples, dry THF was obtained by distillation from calcium hydride under inert atmosphere. Dry DMF and dry CH_2Cl_2 were obtained by storing the reagent grade solvents over 3Å molecular sieves. Determination of reaction pH was estimated by spotting an aliquot from the reaction mixture on wetted E. Merck "colorpHast" pH 1-14 indicator strips. Silica coated TLC plates were used to monitor all reactions (Analtech Uniplate, 2.4 x 10 cm, Silica Gel GF, 250 micron thickness). Pressurized silica gel column chromatography using 230-400 mesh silica gel was performed according to the method of Still, Kahn, and Mitra, J. Org. Chem., 1978, vol. 43, p. 2923. Also, 2,2,2-Trifluoroethyl trifluoromethylsulfonate was prepared by the method of R. L. Hansen, J. Org. Chem., 1965, vol. 30, pp. 4322-4.

All temperatures are degrees Celsius. ^1H NMR spectra were measured at 300 MHz on a Varian XL-300, at 400 MHz on a Varian XL-400, using $(CH_3)_4Si$ as an internal standard All NMR spectra for the compounds of the Examples which follow were consistent with the assigned structures. Fast atom bombardment mass spectra were obtained on a VG-ZAB-HF spectrometer. Analytical HPLC were run on a Spectra Physics SP4270/8800 instrument using the following conditions:

Column: Vydac C_{18}, 0.21 x 15 cm

UV detection at 215 nm

Mobile Phases
A = 0.1% by volume TFA in H_2O
B = 0.1% by volume TFA in acetonitrile
C = 0.1% by volume H_3PO_4 in water
D = 0.1% by volume H_3PO_4 in acetonitrile

Method A:

Gradient
T = 0 min, 95% A, 5% B
T = 15 min, 0% A, 100% B

Flow = 2.0 mL/min

Method B:

Gradient
T = 0 min, 95% A, 5% B
T = 30 min, 5% A, 95% B

Flow = 1.5 mL/min

Method C:

Gradient T = 0 min, 95% C, 5% D
T = 15 min, 5% C, 95% D

Flow = 1.5 mL/min

Method D:

Gradient T = 0 min, 95% A, 5% B
T = 45 min, 5% A, 95% B

Flow = 1.5 mL/min

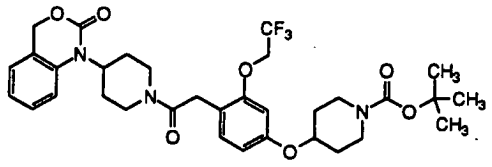
Method E:

Gradient T = 0 min, 95% C, 5% D
T = 15 min, 5% C, 95% D

Flow = 1.5 mL/min

EXAMPLE 1

1-(1-(4-(1-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred, 0°C solution of 4-piperidinone hydrochloride hydrate (50 g, 330 mmol) in DMF (500 mL) was added di-t-butyldicarbonate (64 g, 290 mmol) followed by a dropwise addition of DIEA (63 mL, 360 mmol). After the addition of DIEA was complete, the reaction was allowed to gradually warm to ambient temperature over 4 h and stirring was continued for 20 h. The DMF was removed under

reduced pressure and the residue was dissolved in EtOAc (1000 mL) and washed with 5% aqueous citric acid (2 x 500 mL), water (250 mL), and saturated aqueous $NaHCO_3$ (500 mL). The EtOAc layer was dried (Na_2SO_4), filtered, and the EtOAc was removed under reduced pressure. The residue was boiled in ether (ca. 250 mL) until the solid had dissolved. Cooling gave N-t-butyloxycarbonyl-4-piperidinone as white crystals.

Step 2. N-t-butlyoxycarbonyl-4-piperidinone (20 g, 100 mmol) from Step 1, 2-aminobenzyl alcohol (13 g, 110 mmol), and acetic acid (14 mL, 220 mmol) were dissolved in dry toluene (500 mL). The solution was refluxed under inert atmosphere with azeotropic removal of water for 16 h. The solution was cooled to ambient temperature and to it was added dry THF (200 mL), $NaBH_3CN$ (14 g, 220 mmol), and acetic acid (7 mL, 110 mmol) added dropwise over a period of 30 min. The reaction was stirred at ambient temperature for 24 h. The reaction was concentrated under reduced pressure and the residue was dissolved in EtOAc (750 mL). The EtOAc layer was washed with saturated aqueous $NaHCO_3$ (4 x 500 mL) and brine (250 mL). The EtOAc layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography, using a gradient elution of 15-30% EtOAc-hexanes. 1-t-Butyloxycarbonyl-4-((2-hydroxy-methyl)-phenylamino)piperidine was obtained as a gum.

Step 3. 1-t-Butyloxycarbonyl-4-((2-hydroxymethyl)-phenylamino)-piperidine (24 g, 78 mmol) from Step 2 was dissolved in dry THF (250 mL) and cooled to 0°C. To the solution was added DIEA (41 mL, 240 mmol) and triphosgene (8.54 g, 28.8 mmol). The reaction was stirred at 0°C for 1h, and then at ambient temperature for 72 h. Ether (250 mL) was added, the mixture was cooled to 0°C for 3 h and then filtered to remove the hydrochloride salt of DIEA. The filtrate solvents were removed under reduced pressure and the residue was dissolved in EtOAc (750 mL). The EtOAc solution was washed with 5% aqueous citric acid (2 x 500 mL), water (250 mL), and saturated aqueous $NaHCO_3$ (2 x 500 mL). The EtOAc layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was boiled in ether

(ca. 200 mL) until the solid had dissolved. Cooling overnight gave 1-((1-t-butyloxycarbonyl)piperidin-4-yl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one as off-white crystals.

Step 4. A stirred solution of 1-((1-t-Butyloxycarbonyl)-piperidin-4-yl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one (19 g, 57 mmol) from Step 3 in EtOAc (500 mL) was cooled to 0°C. HCl gas was bubbled through the solution for 30 min. Stirring was continued at 0°C for 1 h, during which time a precipitate had formed, and then at ambient temperature for 1 h. The stirred suspension was cooled to 0°C and cold ether (250 mL) was added. After 1 h at 0°C, the solid was collected by filtration. The solid was dried under reduced pressure for 18 h, giving the hydrochloride salt of 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one as an off-white solid.

Step 5. To a stirred solution of 2,4-dihydroxyacetophenone (6.0 g, 39.5 mmol) and triphenylphosphine (15.5 g, 59.2 mmol) in dry THF (100 mL) at 0°C was added a solution of N-tert-butyloxycarbonyl-4-piperidinol (11.9 g, 59.2 mmol) and DEAD (10.3 g, 59.2 mmol) in dry THF (75 mL) dropwise over a period of 2 h. The mixture was warmed to ambient temperature over 2 h and stirred for an additional 18 h. The solvent was removed under reduced pressure and the residue was suspended in ether. The solid triphenylphosphine oxide was removed by filtration and the filtrate was concentrated under reduced pressure and purified by pressurized silica gel column chromatography using 4:1 hexane:EtOAc as eluant. Concentration of the product-containing fractions gave 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-hydroxyacetophenone as a solid (HPLC retention time = 6.15 min (method A); TLC R_f = 0.49 (1:3 EtOAc:hexanes)).

Step 6. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-hydroxyacetophenone (4.0 g, MW=335, 11.9 mmol) from Step 5 above and 2,2,2-trifluoroethyl trifluoromethylsulfonate (5.4 g, MW=208, 26 mmol) in DMF (50 mL) at 0°C was added Cs_2CO_3 (8.5 g, 26 mmol). The mixture was stirred at 0°C for 2 h and then at ambient temperature for 2h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (150 mL) and saturated aqueous $NaHCO_3$ (200 mL). The organic phase was dried ($MgSO_4$),

filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 4:1 hexanes:EtOAc as eluant. The product-containing fractions were evaporated under reduced pressure to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)acetophenone as a colorless gum (HPLC retention time = 10.6 min (method A); TLC R_f = 0.45 (1:3 EtOAc:hexanes)).

Step 7. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)acetophenone (4.0 g, MW=405, 9.88 mmol) from Step 6 above and trimethyl orthoformate (3.15 g, 29.7 mmol) in MeOH (100 mL) was added thallium trinitrate trihydrate (4.39 g, MW=444.4, 9.88 mmol). The mixture was stirred at ambient temperature for 18 h. A white solid precipitate was removed by filtration and the filtrate solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (200 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. HPLC analysis (method A) of the residue indicated a ca. 4:1 mixture of desired product (retention time = 10.8 min) and product in which the Boc group had been lost (retention time 6.5 min). The residue was dissolved in DMF (20 mL) and di-tert-butyl dicarbonate (0.72 g, 3.3 mmol) was added. The mixture was stirred at ambient temperature for 2 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 4:1 hexanes:EtOAc as eluant. The product-containing fractions were evaporated under reduced pressure to give methyl 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenyl-acetate as a colorless gum (HPLC retention time = 10.8 min (method A); TLC R_f = 0.46 (1:3 EtOAc:hexanes)).

Step 8. To a stirred solution of methyl 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenyl-acetate (3.0 g, MW=435, 6.90 mmol) from Step 7 above in MeOH (25 mL) was added a solution of aqueous NaOH (6.9 mL of a 2.0 N solution, 13.8

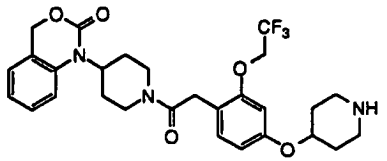
mmol). The mixture was refluxed for 3 h and then cooled to ambient temperature. The solvents were removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (75 mL). The organic phase was separated and washed with H_2O (25 mL) and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetic acid was obtained as an amorphous solid (HPLC retention time = 9.4 min (method A)).

Step 9. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetic acid (2.0 g, MW=421, 4.75 mmol) from Step 8 above, 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (1.3 g, 4.8 mmol) from Step 4 above, and HOBT (0.73g, 4.8 mmol) in DMF (75 mL) was added EDC (2.08 g, 7.1 mmol) and DIEA (1.6 mL, 9.2 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (75 mL). The organic phase was separated and washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (75 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using EtOAc as eluant. The product-containing fractions were evaporated under reduced pressure to give the title compound as an amorphous solid.
HPLC retention time = 10.6 min (method A)
TLC R_f = 0.35 (7:3 EtOAc:hexanes)
FAB MS: m/z = 648 (M^+ + H)
combustion analysis: $C_{33}H_{40}F_3N_3O_7$

Calculated	C, 61.19; H, 6.22; N, 6.49
Found	C, 61.11; H, 6.35; N, 6.37

EXAMPLE 2

1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one

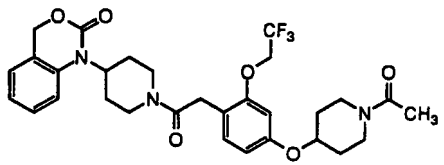


Into a stirred solution of 1-(1-(4-(1-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (3.5 g, 5.4 mmol) from Example 1 in EtOAc (125 mL) at 0°C was bubbled HCl gas for 15 min. The resulting suspension was stirred at 0°C for 45 min. Excess HCl was removed by bubbling argon though the mixture for 15 min. Ether (125 mL) was added and the cold suspension was filtered. The solids were washed with additional ether and then dried under reduced pressure for 18 h to give the hydrochloride salt of the title compound as an amorphous white powder.
HPLC retention time = 7.2 min (method A)
TLC R_f = 0.11 (95:5:0.5 CH_2Cl_2:MeOH:NH_4OH)
FAB MS: m/z = 548 (M^+ + H)
combustion analysis: $C_{28}H_{32}F_3N_3O_5 \cdot 1.4$ HCl, 0.1 EtOAc

Calculated	C, 56.15; H, 5.68; N, 6.92
Found	C, 56.15; H, 5.78; N, 6.92

EXAMPLE 3

1-(1-(4-(1-acetyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



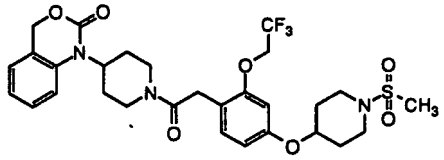
To a solution of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.90 g, 1.5 mmol) from Example 2 in CH_2Cl_2 (50 mL) was added acetic anhydride (0.31 mL, 3.0 mmol) and DIEA (0.52 mL, 3.0 mmol). The solution was stirred at ambient temperature for 1 h and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with 0.25 M aqueous citric acid (50 mL), H_2O (25 mL), and saturated aqueous $NaHCO_3$ (75 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give the title compound as an amorphous solid.

HPLC retention time = 8.9 min (method A)
TLC R_f = 0.27 (97:3 CH_2Cl_2:MeOH)
FAB MS: m/z = 590 ($M^+ + H$)
combustion analysis: $C_{30}H_{34}F_3N_3O_6 \cdot 0.33\ H_2O$

Calculated	C, 60.50; H, 5.87; N, 7.06
Found	C, 60.50; H, 5.86; N, 6.84

EXAMPLE 4

1-(1-(4-(1-methylsulfonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



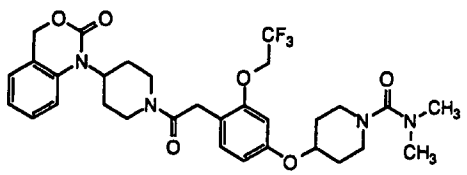
To a solution of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.20 g, 0.35 mmol) from Example 2 in CH_2Cl_2 (20 mL) was added methanesulfonoyl chloride (0.045 g, 0.39 mmol) and DIEA (0.14 mL, 0.80 mmol). The solution was stirred at ambient temperature for 6 h and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with 0.25 M aqueous citric acid (25 mL), H_2O (25 mL), and saturated aqueous $NaHCO_3$ (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 97:3 CH_2Cl_2:MeOH as eluant to give the title compound as an amorphous solid.

HPLC retention time = 16.4 min (method B)
TLC R_f = 0.41 (95:5:0.5 CH_2Cl_2:MeOH:NH_4OH)
FAB MS: m/z = 626 ($M^+ + H$)
combustion analysis: $C_{29}H_{34}F_3N_3O_7S \cdot 0.3\ CH_2Cl_2$, 0.4 MeOH

Calculated	C, 53.73; H, 5.50; N, 6.33
Found	C, 53.70; H, 5.47; N, 6.39

EXAMPLE 5

1-(1-(4-(1-dimethylaminocarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



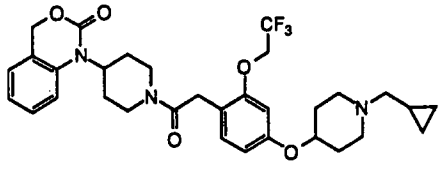
To a solution of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.20 g, 0.35 mmol) from Example 2 in CH_2Cl_2 (20 mL) was added dimethylcarbamoyl chloride (0.042 g, 0.39 mmol) and DIEA (0.14 mL, 0.80 mmol). The solution was stirred at ambient temperature for 6 h and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with 0.25 M aqueous citric acid (25 mL), H_2O (25 mL), and saturated aqueous $NaHCO_3$ (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 97:3 CH_2Cl_2:MeOH as eluant to give the title compound as an amorphous solid.

HPLC retention time = 11.3 min (method B)
TLC R_f = 0.35 (95:5:0.5 CH_2Cl_2:MeOH:NH_4OH)
FAB MS: m/z = 619 ($M^+ + H$)
combustion analysis: $C_{31}H_{37}F_3N_4O_6 \cdot 0.15\ CH_2Cl_2$

Calculated	C, 59.26; H, 5.95; N, 8.87
Found	C, 59.21; H, 5.85; N, 8.92

EXAMPLE 6

1-(1-(4-(1-cyclopropylmethyl-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



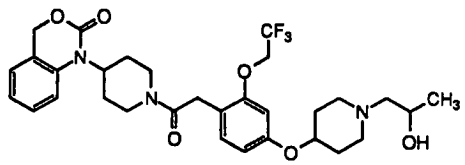
To a solution of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.30 g, 0.5 mmol) from Example 2 in MeOH (7.5 mL) was added sodium acetate (82 mg, 1.0 mmol), acetic acid (0.10 mL, 1.7 mmol), and cyclopropane carboxaldehyde (75 mg, 1.1 mmol). The mixture was stirred at ambient temperature for 30 min and $NaBH_3CN$ (61 mg, 1.0 mmol) was added. The solution was stirred for 18 h and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 97:3:0.3 CH_2Cl_2:MeOH:NH_4OH as eluant. The free base was dissolved in MeOH containing 1.5 equivalents of 3 N aqueous HCl. The resulting solution was evaporated under reduced pressure and the residue was lyophilized from CH_3CN:H_2O to give the hydrochloride salt of the title compound as an amorphous solid.

HPLC retention time = 8.5 min (method A)
TLC R_f = 0.21 (95:5:0.25 CH_2Cl_2:MeOH:NH_4OH)
FAB MS: m/z = 602 ($M^+ + H$)
combustion analysis: $C_{32}H_{38}F_3N_3O_5 \cdot 1.0\ HCl, 0.5\ H_2O$

Calculated	C, 59.39; H, 6.23; N, 6.49
Found	C, 59.34; H, 6.38; N, 6.68

EXAMPLE 7

1-(1-(4-(1-(2-hydroxy-1-propyl)-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



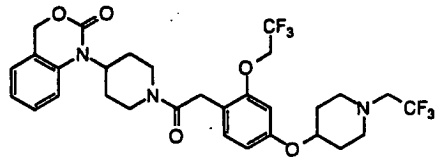
To a solution of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.30 g, 0.5 mmol) from Example 2 in MeOH (10 mL) was added DIEA (0.17 mL, 1.0 mmol) and propylene oxide (1 mL, 13 mmol). The solution was stirred for 18 h at ambient temperature and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 97:3:0.3 CH_2Cl_2:MeOH:NH_4OH as eluant. The free base was dissolved in MeOH containing 1.5 equivalents of 3 N aqueous HCl. The resulting solution was evaporated under reduced pressure and the residue was lyophilized from CH_3CN:H_2O to give the hydrochloride salt of the title compound as an amorphous solid.

HPLC retention time = 7.2 min (method A)
TLC R_f = 0.38 (95:5:0.25 CH_2Cl_2:MeOH:NH_4OH)
FAB MS: m/z = 606 (M^+ + H)
combustion analysis: $C_{31}H_{38}F_3N_3O_6$ •1.0 HCl, 0.5 H_2O

Calculated	C, 57.18; H, 6.19; N, 6.45
Found	C, 57.26; H, 6.23; N, 6.45

EXAMPLE 8

1-(1-(4-(1-(2,2,2-trifluoroethyl)-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



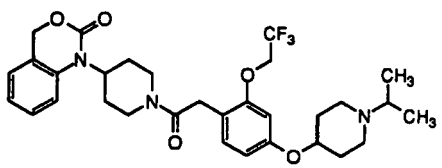
To a stirred solution of the hydrochloride salt of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.20 g, 0.30 mmol) from Example 2 in DMF (3 mL) was added 2,2,2-trifluoroethyl trifluoromethane-sulfonate (0.19 g, 0.9 mmol) and Cs_2CO_3 (0.39 g, 1.2 mmol). The mixture was stirred at ambient temperature for 14 h and then at 50°C for 24 h. The solids were removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPLC using a H_2O:CH_3CN gradient containing 0.1% TFA. The combined product-containing fractions were lyophilized to give the TFA salt of the title compound as an amorphous powder.

HPLC retention time = 19.7 min (method D)
TLC R_f = 0.8 (95:5:0.5 CH_2Cl_2:MeOH:NH_4OH)
FAB MS: m/z = 630 (M^+ + H)
combustion analysis: $C_{30}H_{33}F_6N_3O_5$ •1.0 TFA, 0.1 H_2O

Calculated	C, 51.56; H, 4.62; N, 5.64
Found	C, 51.56; H, 4.48; N, 5.59

EXAMPLE 9

1-(1-(4-(1-(2-propyl)-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



To a stirred solution of the hydrochloride salt of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.20 g, 0.30 mmol) from Example 2 in EtOH (3 mL) was added NaOAc (0.05 g, 0.6 mmol), acetone (0.027 mL, 0.37 mmol), powdered 3 angstrom molecular seives (approx. 100 mg). The mixture was stirred at ambient temperature for 1 h and $NaBH_3CN$ (0.021 mg, 0.34 mmol) was added. The mixture was stirred for 14 h at ambient temperature. More acetone (0.027 mL, 0.37 mmol), molecular seives (approx. 100 mg), and $NaBH_3CN$ (0.021 mg, 0.34 mmol) were added and the mixture was stirred at ambient temperature for 48 h. The mixture was diluted with EtOAc, filtered, and the solvents were removed under reduced pressure. The residue was partitioned between CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was dissolved in EtOH (5 mL) and 1.5 equivalents of 6 N aqueous HCl was added. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (1 mL) and added to a rapidly stirred ether (20 mL). The precipitate was collected by filtration to give the hydrochloride salt of the title compound as an amorphous solid.

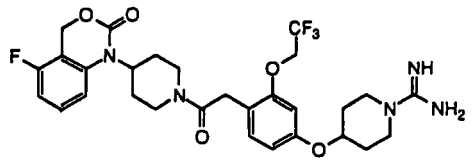
HPLC retention time = 9.8 min (method B)
TLC R_f = 0.25 (95:5:0.5 CH_2Cl_2:MeOH:NH_4OH)

FAB MS: m/z = 590 (M^+ + H)
combustion analysis: $C_{31}H_{38}F_3N_3O_5$ •1.0 HCl, 0.35 CH_2Cl_2, 0.55 Et_2O

Calculated	C, 57.85;	H, 6.54;	N, 6.03
Found	C, 57.86;	H, 6.61;	N, 6.07

EXAMPLE 10

1-(1-(4-(1-carboxamidino-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetyl)piperidin-4-yl)-5-fluoro-4H-3,1-benzoxazin-2(1H)-one



Step 1. N-t-butlyoxycarbonyl-4-piperidinone (1.4 g, 5.74 mmol) from Step 1 of Example 1, 2-amino-6-fluorobenzyl alcohol (0.9 g, 6.4 mmol), and acetic acid (0.758 mL, 12.6 mmol) were dissolved in dry toluene (26 mL). The solution was refluxed under inert atmosphere with azeotropic removal of water for 16 h. The solution was cooled to ambient temperature and to it was added $NaBH_3CN$ (1.1 g, 20.5 mmol) and dry THF (14 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was concentrated under reduced pressure and the residue was dissolved in EtOAc (100 mL). The EtOAc layer was washed with saturated aqueous $NaHCO_3$ (4 x 20 mL) and brine (20 mL). The EtOAc layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 15-30% EtOAc-hexanes. 1-t-Butyloxycarbonyl-4-((2-hydroxy-methyl-3-fluoro)phenylamino)piperidine was obtained as a gum (HPLC retention time = 7.9 min (method A); TLC R_f = 0.80 [10% MeOH(NH_3)/90% CH_2Cl_2]).

Step 2. 1-t-Butyloxycarbonyl-4-((2-hydroxymethyl-3-fluoro)-phenylamino)piperidine (820 mg, 2.5 mmol) from Step 1 above was dissolved in dry THF (8.3 mL) and cooled to 0°C. To the solution was added DIEA (1.3 mL, 7.5 mmol) and triphosgene (250 mg, 0.84 mmol). The reaction was stirred at 0°C for 1h, and then at ambient temperature for 72 h. Ether (10 mL) was added, the mixture was cooled to 0°C for 3 h and then filtered to remove the hydrochloride salt of DIEA. The filtrate solvents were removed under reduced pressure and the residue was dissolved in EtOAc (25 mL). The EtOAc solution was washed with 5% aqueous citric acid (2 x 10 mL), water (10 mL), and saturated aqueous $NaHCO_3$ (2 x 10 mL). The EtOAc layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude solid was purified by pressurized silica gel column chromatography using 98:2 CH_2Cl_2:MeOH(NH_3). The appropriate fractions were combined and the solvent removed under reduced pressure to afford 1-((1-t-butyloxycarbonyl)piperidin-4-yl)-5-fluoro-4(H)-3,1-benzoxazin-2-one as off-white crystals.

Step 3. A stirred solution of 1-((1-t-butyloxycarbonyl)-piperidin-4-yl)-5- fluoro-4(H)-3,1-benzoxazin-2-one (200 mg, 0.57 mmol) from Step 2 above in EtOAc (15 mL) was cooled to 0°C. HCl gas was bubbled through the solution for 30 min. Stirring was continued at 0°C for 1 h, during which time a precipitate had formed, and then at ambient temperature for 1 h. The solvent was removed under reduced pressure to afford a clean product that was dried under reduced pressure for 18 h, giving the hydrochloride salt of 1-(4-piperidinyl)-5-fluoro-4(H)-3,1-benzoxazin-2-one as an off-white solid (HPLC retention time = 4.3 min (method A)).

Step 4. To a solution of 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetic acid (333 mg, 0.77 mmol) from Step 8 of Example 1 in DMF (10 mL) was added EDC (161, mg, 0.84 mmol), HOBT (109 mg, 0.84 mmol) and DIEA (titrated to pH 8, approx 0.12 mL). This solution was stirred for 1 h and then 1-(4-piperidinyl)-5-fluoro-4(H)-3,1-benzoxazin-2-one hydrochloride (200 mg, 0.7 mmol) from Step 3 above was added. The resulting mixture was stirred overnight and then the DMF was removed under reduced

pressure. The crude solid was purified by pressurized silica gel column chromatography using 98:2 CH_2Cl_2:MeOH(NH_3). The appropriate fractions were combined and the solvent was removed under reduced pressure to afford a white foam. The foam was dissolved in 2:1 water:acetonitrile and lyophilized to give 1-(1-(4-(1-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenyl-acetyl)piperidin-4-yl)-5-fluoro-4H-3,1-benzoxazin-2(1H)-one as an amorphous powder (TLC R_f = 0.30 [5% MeOH(NH_3)/95% CH_2Cl_2]; HPLC retention time = 11.3 min (method A)).

Step 5. Into a stirred solution of 1-(1-(4-(1-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenyl-acetyl)-piperidin-4-yl)-5-fluoro-4H-3,1-benzoxazin-2(1H)-one (0.35 g, 0.53 mmol) from Step 4 above in EtOAc (125 mL) at 0°C was bubbled HCl gas for 15 min. The resulting suspension was stirred at 0°C for 45 min. Excess HCl was removed by bubbling argon though the mixture for 15 min. Ether (125 mL) was added and the cold suspension was filtered. The solids were washed with additional ether and then dried under reduced pressure for 18 h to give the hydrochloride salt of of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-5-fluoro-4H-3,1-benzoxazin-2(1H)-one as an amorphous white powder (HPLC retention time = 7.4 min (method A); TLC R_f = 0.15 (95:5:0.5 CH_2Cl_2:MeOH:NH4OH)).

Step 6. To a stirred solution of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-5-fluoro-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.10 g, 0.16 mmol) from Step 5 above in DMF (1 mL) was added 3,5-dimethylpyrazole-1-carboxamidine nitrate (0.034 g, 0.18 mmol) and DIEA (0.063 mL, 0.36 mmol). The solution was stirred at ambient temperature for 48 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using a H_2O:CH_3CN gradient containing 0.1% TFA. The product-containing fractions were combined and lyophilized to give the TFA salt of the title compound as an amorphous powder.
HPLC retention time = 18.7 min (method D)
TLC R_f = 0.10 (90:10:1 CH_2Cl_2:MeOH:NH_4OH)
FAB MS: m/z = 608 (M^+ + H)

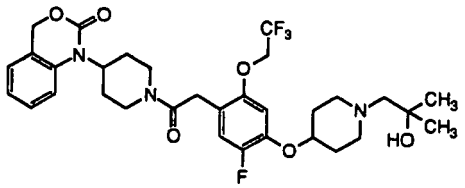
combustion analysis: $C_{29}H_{33}F_4N_5O_5$ •1.15 TFA, 0.95 H_2O

Calculated C, 49.73; H, 4.81; N, 9.27

Found C, 49.77; H, 4.83; N, 8.97

EXAMPLE 11

1-(1-(4-(1-(2-hydroxy-2-methyl)propyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2-(1H)-one



Step 1. To a stirred solution of N-tert-butyloxycarbonyl-4-piperidinol (2.0 g, 10 mmol) in THF (10 mL) at 0°C was added potassium tert-butoxide (10 mL of a 1.0 M solution in THF, 10 mmol) and the solution was stirred for 10 min. The solution was cooled to -78°C and 2,4,5-trifluorobenzonitrile (HPLC retention time = 6.2 min (method A); 2.0 g, 13 mmol) was added. The mixture was stirred at -78°C for 4 h and then allowed to warm to ambient temperature for 10 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and water (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was triturated in ether and the solid was collected to give 4-(N-tert-butyloxycarbonyl-4-pipridinyloxy)-2,5-difluorobenzonitrile (HPLC retention time = 10.1 min (method A)).

Step 2. To a stirred solution of 2,2,2-trifluoroethanol (7.2 g, 8.2 mmol) in THF (10 mL) at 0°C was added potassium tert-butoxide (8.2 mL of a 1.0 M solution in THF, 8.2 mmol). The solution was stirred for

10 min and 4-(N-tert-butyloxycarbonyl-4-pipridinyloxy)-2,5-difluorobenzonitrile (2.5 g, 7.4 mmol) from Step 1 above was added. The solution was stirred at 0°C for 30 min and then at ambient temperature for 12 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and water (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel coulmn chromatography using 20% EtOAc:hexanes as eluant to give 4-(N-tert-butyloxycarbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluorobenzonitrile.

Step 3. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluoro-benzonitrile (2.5 g, 6.2 mmol) from Step 2 above in EtOH (50 mL) was added aqueous NaOH (25 mL of a 3 N solution, 75 mmol). The mixture was refluxed for 48 h. The mixture was diluted with water (50 mL), the volume of solvent was concentrated under reduced pressure to ~ 50 mL, and the mixture was extracted with CH_2Cl_2 (2 x 25 mL). The aqueous phase was acidified to pH 3 with citric acid and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 4-(N-tert-butyloxycarbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluorobenzoic acid as an amorphous solid (HPLC retention time = 10.2 min (method A)).

Step 4. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluorobenzoic acid (1.8 g, 4.2 mmol) from Step 3 above in DMF (25 mL) was added N,O-dimethylhydroxylamine hydrochloride (0.49 g, 5.0 mmol), HOBT (0.64 g, 4.2 mmol), EDC (1.2 g, 6.3 mmol), and DIEA (1.4 mL, 8.0 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (50 mL). The organic layer was washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using 40% EtOAc:hexanes as eluant to give N-methyl,N-methoxy-4-(N-tert-butyloxycarbonyl-4-pipridinyloxy)-2-(2,2,2-

trifluoroethoxy)-5-fluorobenzamide as a colorless gum (HPLC retention time = 18.4 min (method C); TLC R_f = 0.6 (1:1 EtOAc:hexanes)).

Step 5. To a solution of N-methyl,N-methoxy-4-(N-tert-butyloxycarbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluorobenzamide (2.3 g, 4.9 mmol) from Step 4 above in THF (20 mL) at 0°C was added CH_3MgBr (2.5 mL of a 3 M solution in ether, 7.5 mmol). The solution was stirred a 0°C for 1 h and then at ambient temperature for 14 h. Aqueous citric acid (50 mL) was added and the mixture was concetrated under reduced pressure. The residue was partitioned between EtOAc (100 mL) and water (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 30% EtOAc:hexanes as eluant to give 4-(N-tert-butyloxycarbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluoroacetophenone as a colorless gum (HPLC retention time = 21.0 min (method C); TLC R_f = 0.8 (1:1 EtOAc:hexanes)).

Step 6. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluoro-acetophenone (0.90 g, 2.1 mmol) from Step 5 above in MeOH (50 mL) was added trimethyl orthoformate (0.68 mL, 6.2 mmol) and thallium trinitrate trihydrate (0.92 g, 2.1 mmol). The mixture was stirred at ambient temperature for 12 h. The precipitate which had formed was removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was dissolved in DMF (15 mL) and di-tert-butyldicarbonate (0.14 g, 0.63 mmol) was added. The mixture was stirred for 3 h at ambient temperature. The solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 20% EtOAc:hexanes as eluant to give methyl 4-(N-tert-butyloxycarbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluorophenylacetate as a gum (HPLC retention time = 20.6 min (method C); TLC R_f = 0.33 (1:4 EtOAc:hexanes)).

Step 7. To a stirred solution of methyl 4-(N-tert-butyloxycarbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluorophenylacetate (0.86 g, 1.85 mmol) from Step 6 above in MeOH (10 mL) was added aqueous NaOH (4 mL of a 2.7 N solution, 11 mmol). The mixture was stirred at ambient temperature of 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (75 mL) and 0.25 M aqueous citric acid (50 mL). The organic phase was washed with water (25 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 4-(N-tert-butyloxycarbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluorophenylacetic acid as an amorphous solid (HPLC retention time = 11.3 min (method C)).

Step 8. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-pipridinyloxy)-2-(2,2,2-trifluoroethoxy)-5-fluoro-phenylacetic acid (0.50 g, 1.1 mmol) from Step 7 above, 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.31 g, 1.1 mmol) from Step 4 of Example 1, and HOBT (0.17 g, 1.1 mmol) in DMF (10 mL) was added EDC (0.33 g, 1.7 mmol) and DIEA (1.6 mL, 9.2 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (75 mL). The organic phase was separated and washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (75 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 98:2 CH_2Cl_2:MeOH as eluant. The product-containing fractions were evaporated under reduced pressure to give 1-(1-(4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as an amorphous solid (HPLC retention time = 12.2 min (method B); TLC Rf = 0.62 (95:5 CH_2Cl_2:MeOH)).

Step 9. Into a stirred solution of 1-(1-(4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.55 g, 0.83 mmol) from Step 8 above in EtOAc (50 mL) at 0°C was bubbled HCl gas for 15 min. The

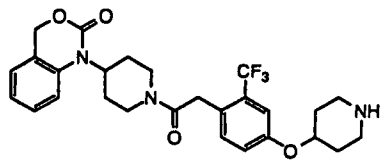
resulting suspension was stirred at 0°C for 45 min. Excess HCl was removed by bubbling argon though the mixture for 15 min. Ether (50 mL) was added and the cold suspension was filtered. The solids were washed with additional ether and then dried under reduced pressure for 18 h to give the hydrochloride salt of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as an amorphous white powder (HPLC retention time = 8.2 min (method B); TLC R_f = 0.14 (90:10:0.5 CH_2Cl_2:MeOH:NH_4OH)).

Step 10. To a solution of the free base of 1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.15 g, 0.27 mmol) from Step 9 above in MeOH(5 mL) was added isobutylene oxide (1 mL). The solution was kept at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using a H_2O:CH_3CN gradient containing 0.1% TFA. The product-containing fractions were combine and lyophilized to give the TFA salt of the title compound as an amorphous white powder.
HPLC retention time = 8.7 min (method B)
TLC R_f = 0.42 (95:5:0.5 CH_2Cl_2:MeOH:NH_4OH)
FAB MS: m/z = 638 (M^+ + H)

combustion analysis: $C_{32}H_{39}F_5N_3O_6$ •1.55 TFA, 0.15 H_2O
Calculated C, 51.60; H, 5.04; N, 5.14
Found C, 51.61; H, 5.05; N, 5.03

EXAMPLE 12

1-(1-(4-(4-piperidinyloxy)-2-trifluoromethylphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of N-tert-butyloxycarbonyl-4-piperidinol (1.0 g, 5.0 mmol) in THF (20 mL) at 0°C was added potassium tert-butoxide (5.0 mL of a 1.0 M solution in THF, 5.0 mmol). The mixture was stirred for 10 min and 4-fluoro-2-trifluoromethyl-benzonitrile (1.04 g, 5.5 mmol) was added. The mixture was stirred at 0°C for 1 h and then at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:2 EtOAc:hexanes as eluant to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-trifluoromethylbenzonitrile as a colorless gum.

Step 2. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-trifluoromethylbenzonitrile (1.5 g, 3.7 mmol) from Step 1 above in EtOH (25 mL) was added aqueous NaOH (2.3 g, 57 mmol in 15 mL of water). The mixture was heated to reflux for 48 h. Water was added (50 mL) and the volume was concentrated under reduced pressure

to ~ 50 mL. The mixture was extracted with CH_2Cl_2 (2 x 25 mL) and the aqueous phase was acidified to pH 3 by the addition of 5 N aqueous HCl. The mixture was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-trifluoromethylbenzoic acid as an amorphous solid (HPLC retention time = 10.0 min (method A)).

Step 3. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-trifluoromethylbenzoic acid (0.66 g, 2.3 mmol) from Step 2 above in THF (10 mL) at 0°C was added BH_3•THF complex (3.5 mL of a 1.0 M solution in THF, 3.5 mmol). The solution was stirred at 0°C for 1 h and then at ambient temperature for 14 h. The solution was diluted with saturated aqueous $NaHCO_3$ (25 mL) and the solvents were removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and water (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-trifluoromethylbenzyl alcohol as a colorless gum (HPLC retention time = 10.2 min (method A)).

Step 4. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-trifluoromethylbenzyl alcohol (0.63 g, 1.7 mmol) from Step 3 above in ether (10 mL) at 0°C was added CBr_4 (0.85 g, 2.6 mmol) and triphenylphosphine (0.68 g, 2.6 mmol). The mixture was stirred at 0°C for 30 min and then at ambient temperature for 14 h. The ether solution was decanted away from the gummy precipitate of triphenylphosphine oxide that had formed and the solvent was removed unde reduced pressure. The residue was purified by pressurized silica gel column chromatography using 5% EtOAc:hexanes as eluant to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-trifluoromethylbenzyl bromide as a colorless gum (HPLC retention time = 12.6 min (method A)).

Step 5. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-trifluoromethylbenzyl bromide (0.37 g, 0.87 mmol) from Step 4 above in DMF (4 mL) was added NaCN (0.064 g, 1.3 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-trifluoromethylphenylacetonitrile was a pale yellow gum (HPLC retention time = 11.4 min (method A)).

Step 6. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-trifluoromethylphenylacetonitrile (0.26 g, 0.87 mmol) from Step 5 above in acetic acid (10 mL) was added concentrated aqueous HCl (5 mL). The mixture was refluxed for 4 h. The solvents were removed under reduced pressure and the residue was stripped from DMF (2 x). The residue was then dissolved in DMF (5 mL). DIEA (0.45 mL, 2.6 mmol) and di-tert-butyldicarbonate (0.21 g, 9.6 mmol) were added. The mixture was stirred at ambient temperature for 3 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was washed with water (2 x 25 mL), dried ($MgSO_4$), filtered, and the solvent was removed under redcued pressure to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-trifluoromethylphenylacetic acid as an amorphous solid (HPLC retention time = 10.1 min (method A)).

Step 7. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-trifluoromethylphenylacetic acid (0.20 g, 0.51 mmol) from Step 6 above, 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.15 g, 0.56 mmol) from Step 4 of Example 1, and HOBT (0.076 g, 0.5 mmol) in DMF (5 mL) was added EDC (0.18 g, 0.96 mmol) and DIEA (0.17 mL, 1.0 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (10 mL), saturated aqueous $NaHCO_3$ (25 mL), and

brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 97:3 CH_2Cl_2:MeOH as eluant to give 1-(1-(4-(1-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(trifluoromethyl)phenyl-acetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as an amorphous solid (HPLC retention time = 11.5 min (method A); TLC R_f = 0.8 (9:1 CH_2Cl_2:MeOH)).

Step 8. Into a stirred solution of 1-(1-(4-(1-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(trifluoromethyl)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.35 g, 0.51 mmol) from Step 7 above in EtOAc (25 mL) at 0°C was bubbled HCl gas for 15 min. The resulting suspension was stirred at 0°C for 45 min. Excess HCl was removed by bubbling argon though the mixture for 15 min. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The solvent was evaporated under reduced pressure to give the hydrochloride salt of the title compound as an amorphous solid.

HPLC retention time = 7.3 min (method A)

TLC R_f = 0.2 (90:10:0.5 CH_2Cl_2:MeOH:NH_4OH)

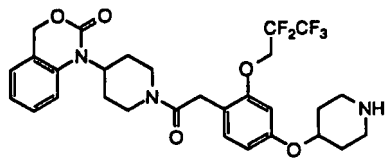
FAB MS: m/z = 518 (M^+ + H)

combustion analysis: $C_{27}H_{30}F_3N_3O_4$ •2.1 HCl, 0.1 CH_2Cl_2

Calculated	C, 54.00; H, 5.40; N, 6.97
Found	C, 54.02; H, 5.15; N, 7.10

EXAMPLE 13

1-(1-(4-(4-piperidinyloxy)-2-(2,2,3,3,3-pentafluoropropyloxy)phenyl-acetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-hydroxyacetophenone (0.50 g, 1.5 mmol) from Step 5 of Example 1 and 2,2,3,3,3-pentafluoropropyl trifluoromethylsulfonate (0.775 g, 3.0 mmol) in DMF (5 mL) at 0°C was added Cs_2CO_3 (0.97 g, 3.0 mmol). The mixture was stirred at 0°C for 2 h and then at ambient temperature for 12 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 4:1 hexanes:EtOAc as eluant. The product-containing fractions were evaporated under reduced pressure to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,3,3,3-pentafluoropropyloxy)acetophenone as a colorless gum (HPLC retention time = 11.6 min (method A); TLC R_f = 0.26 (1:4 EtOAc:hexanes)).

Step 2. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(2,2,3,3,3-pentafluoropropyloxy)-acetophenone (0.45 g, 1.0 mmol) from Step 1 above and trimethyl orthoformate (0.32 g, 3.0 mmol) in MeOH (15 mL) was added thallium trinitrate trihydrate (0.45 g, 1.0 mmol). The mixture was stirred at ambient temperature for 18 h. A white solid precipitate was removed by filtration and the filtrate solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (25

mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. HPLC analysis (method A) of the residue indicated a ca. 4:1 mixture of desired product (retention time = 11.7 min) and product in which the Boc group had been lost (retention time 7.1 min). The residue was dissolved in DMF (3 mL) and di-tert-butyl dicarbonate (0.087 g, 0.40 mmol) was added. The mixture was stirred at ambient temperature for 2 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 4:1 hexanes:EtOAc as eluant. The product-containing fractions were evaporated under reduced pressure to give methyl 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,3,3,3-pentafluoro-propyloxy)phenylacetate as a colorless gum (HPLC retention time = 11.7 min (method A); TLC R_f = 0.30 (1:4 EtOAc:hexanes)).

Step 3. To a stirred solution of methyl 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(2,2,3,3,3-pentafluoropropyloxy)phenyl-acetate (0.40 g, 0.82 mmol) from Step 2 above in MeOH (5 mL) was added a solution of aqueous NaOH (0.82 mL of a 2.0 N solution, 1.6 mmol). The mixture was refluxed for 3 h and then cooled to ambient temperature. The solvents were removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. 4-(N-tert-Butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,3,3,3-pentafluoropropyloxy)phenylacetic acid was obtained as an amorphous solid (HPLC retention time = 9.7 min (method A)).

Step 4. To a stirred solution of (N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,3,3,3-pentafluoropropyloxy)phenylacetic acid (0.30 g, 0.64 mmol) from Step 3 above, 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.17 g, 0.64 mmol) from Step 4 of Example 1, and HOBT (0.098 g, 0.64 mmol) in DMF (5 mL) was added

EDC (0.18 g, 0.96 mmol) and DIEA (0.17 mL, 1.0 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (10 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using EtOAc as eluant. The product-containing fractions were evaporated under reduced pressure to give 1-(1-(4-(1-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,3,3,3-pentafluoro-propyloxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as an amorphous solid (HPLC retention time = 11.7 min (method A); TLC R_f = 0.75 (EtOAc)).

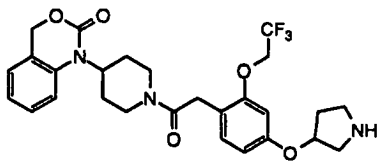
Step 5. Into a stirred solution of 1-(1-(4-(1-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(2,2,3,3,3-pentafluoropropyloxy)phenyl-acetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.35 g, 0.53 mmol) from Step 4 above in EtOAc (25 mL) at 0°C was bubbled HCl gas for 15 min. The resulting suspension was stirred at 0°C for 45 min. Excess HCl was removed by bubbling argon though the mixture for 15 min. Ether (50 mL) was added and the cold suspension was filtered. The solids were washed with additional ether and then dried under reduced pressure for 18 h to give the hydrochloride salt of the title compound as an amorphous white powder.

HPLC retention time = 7.9 min (method A)
TLC R_f = 0.25 (90:10:0.5 CH_2Cl_2:MeOH:NH4OH)
FAB MS: m/z = 548 ($M^+ + H$)
combustion analysis: $C_{29}H_{32}F_5N_3O_5 \cdot 1.4\ HCl, 0.3\ H_2O$

Calculated	C, 54.47; H, 5.30; N, 6.57
Found	C, 54.45; H, 5.41; N, 6.63

EXAMPLE 14

1-(1-(4-(3-pyrrolidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Steps 1-4. 4-(N-tert-Butyloxycarbonyl-3-pyrrolidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetic acid (HPLC retention time = 9.3 min (method A) was synthesized in 4 steps from 2,4-dihydroxy-acetophenone, N-tert-butyloxycarbonyl-3-pyrrolidinol, and 2,2,2-trifluoroethyl trifluoromethylsulfonate using procedures analogous to those given in Steps 5-8 of Example 1.

Steps 5-6. 4-(N-tert-Butyloxycarbonyl-3-pyrrolidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetic acid and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride from Step 4 of Example 1 were converted to the title compound using procedures analogous to those given in Example 1 (step 9) and Example 2. The hydrochloride salt of the title compound was obtained as an amorphous powder by precipitation from ether.

HPLC retention time = 7.2 min (method A)

TLC R_f = 0.50 (90:10:0.5 CH_2Cl_2:MeOH:NH_4OH)

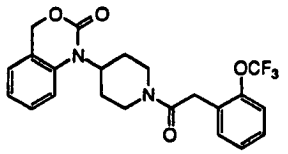
FAB MS: m/z = 534 ($M^+ + H$)

combustion analysis: $C_{27}H_{30}F_3N_3O_5 \cdot 1.0\ HCl, 1.0\ H_2O$

Calculated	C, 55.15; H, 5.66; N, 7.15
Found	C, 55.53; H, 5.70; N, 7.08

EXAMPLE 15

1-(1-(2-trifluoromethoxyphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 2-trifluoromethoxybenzoic acid (1.0 g, 5.2 mmol) in THF (25 mL) at 0°C was added borane-THF complex (15 mL of a 1.0 M solution in THF, 15 mmol). The solution was warmed to ambient temperature and stirred for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (75 mL) and saturated aqueous $NaHCO_3$ (75 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give 2-trifluoromethoxybenzyl alcohol as a colorless liquid (TLC R_f = 0.2 (1:3 EtOAc-hexanes)).

Step 2. To a stirred solution of 2-trifluoromethoxybenzyl alcohol (0.81 g, 4.5 mmol) from Step 1 above in ether (20 mL) at 0°C was added triphenylphosphine (2.4 g, 9.2 mmol) and CBr_4 (3.0 g, 9.2 mmol). The mixture was warmed to ambient temperature and stirred for 18 h. The ether was decanted from the gummy precipitate of triphenylphosphine oxide and evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using hexanes as eluant to give 2-trifluoromethoxybenzyl bromide as a colorless liquid (TLC R_f = 0.80 (hexanes)).

Step 3. To a stirred solution of 2-trifluoromethoxybenzyl bromide (0.95 g, 3.9 mmol) from Step 2 above in DMF (5 mL) was added NaCN (0.21 g, 4.3 mmol). The mixture was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column

chromatography using 15% EtOAc-hexanes as eluant to give 2-trifluoromethoxyphenylacetonitrile as a colorless liquid (TLC R_f = 0.6 (solvent)).

Step 4. 2-Trifluoromethoxyphenylacetonitrile (0.49 g, 2.6 mmol) from Step 3 above was refluxed for 3 h in a 1:1 mixture of acetic acid and concentrated aqueous HCl. The solvents were removed under reduced pressure. The residue was partitioned between EtOAc (75 mL) and water (2 x 25 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 2-trifluoromethoxyphenylacetic acid as an amorphous solid (HPLC retention time = 6.8 min (method A)).

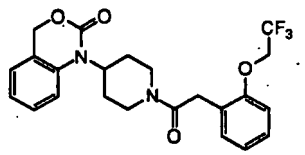
Step 5. To a stirred solution of 2-trifluoromethoxyphenylacetic acid (0.20 g, 0.96 mmol) from Step 4 above and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.26 g, 0.96 mmol) from Step 4 of Example 1 in DMF (15 mL) was added HOBT (0.15 g, 1.0 mmol), EDC (0.44 g, 1.5 mmol), and DIEA (0.3 mL, 1.7 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using EtOAc as eluant. The product-containing fractions were evaporated under reduced pressure to give the title compound as an amorphous solid.

HPLC retention time = 9.5 min (method A)
TLC R_f = 0.40 (2:1 EtOAc:hexanes)
FAB MS: m/z = 435 ($M^+ + H$)
combustion analysis: $C_{22}H_{21}F_3N_2O_4$

Calculated	C, 60.83; H, 4.87; N, 6.45
Found	C, 60.85; H, 4.89; N, 6.36

EXAMPLE 16

1-(1-(2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of methyl 2-hydroxyphenylacetate (10 g, 60 mmol) in DMF (150 mL) at 0°C was added 2,2,2-trifluoroethyl trifluoromethansulfonate (94 mmol) and Cs_2CO_3 (38 g, 120 mmol). The mixture was stirred at 0°C for 2 h and then at ambient temperature for 12 h. The solids were removed by filtration and the filtrate solvents were removed under reduced pressure. The residue was partitioned between EtOAc (250 mL) and water (2 x 100 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to give methyl 2-(2,2,2-trifluoroethoxyphenylacetate as a colorless liquid (HPLC retention time = 9.3 min (method E); TLC R_f = 0.6 (2:1 hexanes:EtOAc)).

Step 2. To a stirred solution of methyl 2-(2,2,2-trifluoroethoxyphenylacetate (2 g, 8 mmol) from Step 1 above in DME (20 mL) was added aqueous LiOH (20 mL of a 1.0 M solution, 20 mmol). The solution was stirred at ambient temperature for 1 h. The solution was concentrated under reduced pressure to ~10 mL and 0.25 M aqueous citric acid (20 mL) was added. The precipitate was removed by filtration and dried under reduced pressure to give 2-(2,2,2-trifluoroethoxyphenylacetic acid as a crystalline solid (HPLC retention time = 7.4 min (method E)).

Step 3. To a stirred solution of 2-(2,2,2-trifluoroethoxy-phenylacetic acid (0.20 g, 0.90 mmol) from Step 2 above and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.24 g, 0.90 mmol) from Step 4 of Example 1 in DMF (15 mL) was added HOBT (0.15 g, 1.0 mmol), EDC (0.44 g, 1.5 mmol), and DIEA (0.3 mL, 1.7 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (5 mL) and cooled to 0°C to give the title compound as a crystalline solid.

HPLC retention time = 9.7 min (method A)

TLC R_f = 0.6 (4:1 EtOAc:hexanes)

FAB MS: m/z = 449 ($M^+ + H$)

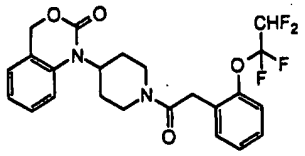
combustion analysis: $C_{23}H_{23}F_3N_2O_4$

Calculated C, 61.60; H, 5.17; N, 6.25

Found C, 61.53; H, 5.07; N, 6.21

EXAMPLE 17

1-(1-(2-(1,1,2,2-tetrafluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 2-(1,1,2,2-tetrafluoro-ethoxy)toluene (2.5 g, 12.2 mmol) in CCl_4 (75 mL) was added NBS (2.1 g,

13 mmol) and AIBN (0.65 g, 3 mmol). The mixture was relfuxed for 6 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (75 mL) and water (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using hexanes as eluant to give 2-(1,1,2,2-tetrafluoroethoxy)benzyl bromide as a colorless liquid (TLC R_f = 0.7 (hexanes)).

Step 2. To a stirred solution of 2-(1,1,2,2-tetrafluoro-ethoxy)benzyl bromide (1.0 g, 3.5 mmol) from Step 1 above in DMF (5 mL) was added NaCN (0.18 g, 3.7 mmol). The mixture was stirred at ambient temperature for 48 h and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 5-10% EtOAc:hexanes to give 2-trifluoromethoxyphenylacetonitrile as a colorless liquid (HPLC retention time = 9.0 min (method A); TLC R_f = 0.18 (5% EtOAc:hexanes)).

Step 3. 2-(1,1,2,2-Tetrafluoroethoxy)phenylacetonitrile (0.49 g, 2.4 mmol) from Step 2 above was refluxed for 3 h in a 1:1 mixture of acetic acid and concentrated aqueous HCl. The solvents were removed under reduced pressure. The residue was partitioned between EtOAc (75 mL) and water (2 x 25 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 2-(1,1,2,2-tetrafluoroethoxy)phenylacetic acid as an amorphous solid (HPLC retention time = 7.7 min (method A)).

Step 4. To a stirred solution of 2-(1,1,2,2-tetrafluoro-ethoxy)phenylacetic acid (0.20 g, 0.92 mmol) from Step 3 above and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (1.3 g, 4.8 mmol) from Step 4 of Example 1 in DMF (15 mL) was added HOBT (0.15 g, 1.0 mmol), EDC (0.44 g, 1.5 mmol), and DIEA (0.3 mL, 1.7 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The organic phase was

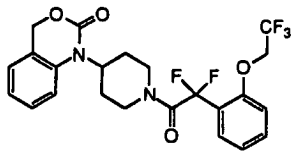
dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using EtOAc as eluant. The product-containing fractions were evaporated under reduced pressure to give the title compound as an amorphous solid.

HPLC retention time = 9.6 min (method A)
TLC R_f = 0.56 (4:1 EtOAc:hexanes)
FAB MS: m/z = 435 ($M^+ + H$)
combustion analysis: $C_{23}H_{22}F_4N_2O_4$

Calculated	C, 59.23; H, 4.75; N, 6.01
Found	C, 59.13; H, 4.84; N, 6.05

EXAMPLE 18

1-(1-(2-(2,2,2-trifluoroethoxy)phenyldifluoroacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. A solution of methyl 2-(2,2,2-trifluoroethoxy)-phenylacetate (0.30 g, 1.2 mmol) from Step 1 of Example 16 in THF (12 mL) was cooled to -78°C under inert atmosphere. To this solution was added potassium hexamethyldisilazide (4.32 mmol of a 0.5 M in THF) and the reaction was stirred for 1 h. A solution of 2-fluoro-3,3-dimethyl-1,2-benzisothiazole (4.32 mmol, 929 mg) in THF (3 mL) was then added dropwise. The solution was stirred for 1 h at -78°C and then allowed to warm to ambient temperature. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), concentrated under reduced pressure, and extracted with CH_2Cl_2 (30 mL). The organic layer was

dried over $MgSO_4$ and filtered. Evaporation of the solvents gave an oily residue. The crude product was purified by pressurized silica gel column chromatography (silica gel treated with 2% TEA:hexanes and eluted with 10% ethyl acetate/hexane) which provided methyl 2-(2,2,2-trifluoroethoxy)phenyl)difluoroacetate as a white foam after evaporation of the hexanes/ethyl acetate mixture (HPLC retention time = 8.7 min (method A); TLC Rf = 0.85 (40% EtOAc:hexanes)).

Step 2. Methyl 2-(2,2,2-trifluoroethoxy)phenyl)-difluoro-acetate (40 mg, 0.14 mmol) from Step 1 above was dissolved in 4:1 THF:H_2O (1.25 mL total) and treated with $LiOH \cdot H_2O$ (5 mg, 0.14 mmol) at ambient temperature under inert atmosphere. The solution was stirred 4 h and then 5N HCl was added and the solvent was removed under reduced pressure to afford 2-(2,2,2-trifluoroethoxy)phenyl)-difluoroacetic acid.

Step 3. To a solution 2-(2,2,2-trifluoroethoxy)phenyl)-difluoroacetic acid (40 mg, 0.15 mmol) from Step 2 above in DMF (0.75 mL) was added EDC (35 mg, 0.18 mmol), HOBT (28 mg, 0.18 mmol) and DIEA (titrated to pH 8, approx 0.05 mL). This solution was stirred for 1 h and then 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (45 mg, 0.17 mmol) from Step 4 of Example 1 was added. The resulting mixture was stirred for 14 h. The DMF was removed under reduced pressure. The crude solid was purified by pressurized silica gel column chromatography using 98:2 CH_2Cl_2:MeOH(NH_3). The appropriate fractions were combined and the solvent removed under reduced pressure to afford a white foam. The foam was dissolved in 2:1 water:acetonitrile and lyophilized to give the title compound as an amorphous powder

TLC: R_f = 0.60 [10% MeOH(NH_3)/90% CH_2Cl_2]
HPLC (method A): retention time 9.56 min.
FAB MS : m/z 485 ($M^+ + H$)

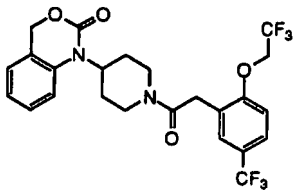
combustion analysis: $C_{23}H_{21}F_5N_2O_4 \cdot 0.35\ H_2O$, 0.15 CH_3CN

Calculated C, 56.32; H, 4.49; N, 6.06

Found C, 56.36; H, 4.56; N, 6.03

EXAMPLE 19

1-(1-(2-(2,2,2-trifluoroethoxy)-5-trifluoromethylphenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 2,2,2-trifluoroethanol (0.53 mL, 7.3 mmol) in THF (20 mL) at 0°C was added potassium tert-butoxide (7.3 mL of a 1.0 M solution in THF, 7.3 mmol). The mixture was stirred at 0°C for 10 min and 2-fluoro-5-trifluoromethyl-acetophenone (1.0 g, 4.9 mmol; HPLC retention time = 8.7 min (method A)) was added. The mixture was stirred at 0°C for 15 min and then at ambient temperature for 5 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 2-(2,2,2-trifluoroethoxy)-5-trifluoromethylacetophenone as a gum (HPLC retention time = 10.0 min (method A)).

Step 2. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-5-trifluoromethylacetophenone (0.97 g, 3.4 mmol) from Step 1 above in MeOH (17 mL) was added trimethyl orthoformate (1.1 mL, 1.1 mmol) and thallium trinitrate trihydrate (1.5 g, 3.4 mmol). The mixture was stirred at ambient temperature for 48 h. The precipitate which had

formed was removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give methyl 2-(2,2,2-trifluoroethoxy)-5-trifluoromethylphenylacetate as a gum (HPLC retention time = 10.0 min (method A)).

Step 3. To a stirred solution of methyl 2-(2,2,2-trifluoroethoxy)-5-trifluoromethylphenylacetate (1.07 g, 3.5 mmol) from Step 2 above in THF (8 mL) and water (2 mL) was added LiOH (0.20 g, 4.8 mmol). The mixture was stirred at ambient temperature for 24 h. The reaction was acidified to pH 2 with 5 N aqueous HCl and the solvents were removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 0-50% MeOH:CH_2Cl_2 to give 2-(2,2,2-trifluoroethoxy)-5-trifluoromethylphenylacetic acid as a gum (HPLC retention time = 8.7 min (method A)).

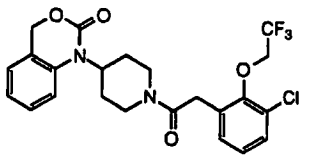
Step 4. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-5-trifluoromethylphenylacetic acid (0.10 g, 0.33 mmol) from Step 3 above, 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.10 g, 0.36 mmol) from Step 4 of Example 1, and HOBT (0.06 g, 0.4 mmol) in DMF (5 mL) was added EDC (0.10 g, 0.5 mmol) and DIEA (0.088 mL, 0.5 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using a H_2O:CH_3CN gradient containing 0.1% TFA. The product-containing fractions were lyophilized to give the title compound as an amorphous powder.
HPLC retention time = 10.1 min (method A)
TLC R_f = 0.85 (90:10 CH_2Cl_2:MeOH)
FAB MS: m/z = 517 ($M^+ + H$)
combustion analysis: $C_{24}H_{22}F_6N_2O_4 \cdot 0.65\ H_2O$

Calculated C, 54.58; H, 4.45; N, 5.30

Found C, 54.56; H, 4.10; N, 5.20

EXAMPLE 20

1-(1-(2-(2,2,2-trifluoroethoxy)-3-chlorophenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a solution of 2-hydroxy-3-chlorotoluene (5 g, 35 mmol) in DMF (75 mL) at 0°C was added 2,2,2-trifluoroethoxy trifluoromethylsulfonate (16 g, 70 mmol) and Cs_2CO_3 (22 g, 68 mmol). The mixture was stirred at 0°C for 3 h and then at ambient temperature for 14 h. The solvent was removed under reduced pressure. The residue was partitioned between EtOAc (150 mL) and water (3 x 75 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:4 EtOAc:hexanes as eluant to give 2-(2,2,2-trifluoroethoxy)-3-chlorotoluene as an oil.

Step 2. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-3-chlorotoluene (2.4 g, 11 mmol) from Step 1 above in CCl_4 (40 mL) was added NBS (2.1 g, 11 mmol) and AIBN (1.8 g, 11 mmol). The mixture was refluxed for 8 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using hexanes as eluant. 2-(2,2,2-trifluoroethoxy)-3-chlorobenzyl bromide was obtained as an oil (HPLC retention time = 22.3 min (method D)).

Step 3. To a solution of 2-(2,2,2-trifluoroethoxy)-3-chlorobenzyl bromide (1.6 g, 5.4 mmol) from Step 2 above in DMF (12 mL) was added NaCN (0.28 g, 5.7 mmol). The solution was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and saturated aqueous

$NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 5-20% EtOAc:hexanes to give 2-(2,2,2-trifluoroethoxy)-3-chlorophenylacetonitrile as a colorless oil.

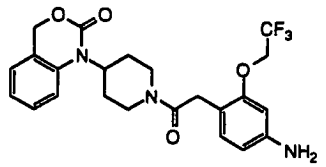
Step 4. 2-(2,2,2-trifluoroethoxy)-3-chlorophenyl-acetonitrile (1.2 g, 5.1 mmol) from Step 3 above was refluxed in a 2:1 mixture of acetic acid and concentrated aqueous HCl (25 mL) for 12 h. The solvents were removed under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was washed with water, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 2-(2,2,2-trifluoroethoxy)-3-chlorophenylacetic acid as an oil.

Step 5. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-3-chlorophenylacetic acid (0.14 g, 0.53 mmol) from Step 4 above, 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.14 g, 0.53 mmol) from Step 4 of Example 1, and HOBT (0.08 g, 0.53 mmol) in DMF (5 mL) was added EDC (0.15 g, 0.8 mmol) and DIEA (0.14 mL, 0.8 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using a H_2O:CH_3CN gradient containing 0.1% TFA. The product-containing fractions were lyophilized to give the title compound as an amorphous powder.
HPLC retention time = 25.6 min (method D)
TLC R_f = 0.74 (95:5 CH_2Cl_2:MeOH)
FAB MS: m/z = 482 ($M^+ + H$)
combustion analysis: $C_{23}H_{22}ClF_3N_2O_4 \cdot 0.55$ TFA, 0.15 H_2O

Calculated	C, 56.44; H, 4.49; N, 5.46
Found	C, 56.43; H, 4.48; N, 5.54

EXAMPLE 21

1-(1-(2-(2,2,2-trifluoroethoxy)-4-aminophenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 4-nitro-2-hydroxytoluene (5 g, 33 mmol) in DMF (75 mL) at 0°C was added 2,2,2-trifluoroethyl trifluoromethylsulfonate (13 g, 62 mmol) and Cs_2CO_3 (20 g, 62 mmol). The mixture was stirred at 0°C for 30 min and then at ambient temperature for 2 h. The mixture was diluted with EtOAc (150 mL) and filtered. The filtrate solvents were removed under reduced pressure and the residue was dissolved in EtOAc (200 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered, and the volume was reduced to ~50 mL under reduced pressure, at which point the product had begun to crystallize. The mixture was cooled to -20°C for 14 h, filtered, and the solids were washed with cold EtOAc. 4-Nitro-2-(2,2,2-trifluoroethoxy)toluene was obtained as a crystalline solid (HPLC retention time = 10.0 min (method A)).

Step 2. 4-Nitro-2-(2,2,2-trifluoroethoxy)toluene (2.0 g, 9.0 mmol) from Step 1 above was dissolved in MeOH (20 mL) and shaken with palladium black (100 mg) under 50 psig of hydrogen on a Parr apparatus for 2 h. The catalyst was removed by filtration and the solvent was removed under reduced pressure to give 4-amino-2-(2,2,2-trifluoroethoxy)toluene as a gum.

Step 3. To a stirred solution of 4-amino-2-(2,2,2-trifluoroethoxy)toluene (1.2 g, 6.2 mmol) from Step 2 above in DMF (20 mL) was added di-tert-butyldicarbonate (3.4 g, 16 mmol) and DMAP (0.76 g, 6.2 mmol). The mixture was stirred at ambient temperature for 2 h and then at 40°C for 14 h. The solvent was removed under reduced

pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (75 mL). The organic phase was separated, washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 5-15% EtOAc:hexanes to give 4-(N,N-di-(tert-butylcarbonyl)amino)-2-(2,2,2-trifluoroethoxy)toluene as a colorless gum (TLC R_f = 0.55 (15% EtOAc:hexanes)).

Step 4. To a stirred solution of 4-(N,N-di-(tert-butyl-carbonyl)amino)-2-(2,2,2-trifluoroethoxy)toluene (2.0 g, 5.0 mmol) from Step 3 above in CCl_4 (75 mL) was added NBS (0.90 g, 5.0 mmol) and AIBN (0.2 g, 1.2 mmol). The mixture was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 5-15% EtOAc:hexanes to give 4-(N,N-di-(tert-butyl-carbonyl)amino)-2-(2,2,2-trifluoroethoxy)benzyl bromide as a colorless gum (TLC R_f = 0.50 (15% EtOAc:hexanes)).

Step 5. To a stirred solution of 4-(N,N-di-(tert-butyl-carbonyl)amino)-2-(2,2,2-trifluoroethoxy)benzyl bromide (1.5 g, 3.2 mmol) from Step 4 above in DMF (20 mL) was added NaCN (0.23 g, 4.8 mmol). The mixture was stirred at ambient temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 15% EtOAc:hexanes as eluant to give an inseparable mixture (~3:1) of 4-(N,N-di-(tert-butylcarbonyl)amino)-2-(2,2,2-trifluoroethoxy)phenyl-acetonitrile and 4-(tert-butylcarbonylamino)-2-(2,2,2-trifluoroethoxy)-phenylacetonitrile (TLC R_f = 0.28 (15% EtOAc:hexanes)).

Step 6. A ~3:1 mixture of 4-(N,N-di-(tert-butylcarbonyl)-amino)-2-(2,2,2-trifluoroethoxy)phenylacetonitrile and 4-(tert-butyl-carbonylamino)-2-(2,2,2-trifluoroethoxy)phenylacetonitrile (1.1 g) from Step 5 above was refluxed in a 1:1 mixture of acetic acid and concentrated aqueous HCl for 3 h. The solvents were removed under

reduced pressure. The residue was dissolved in water and the solvent was evaporated under reduced pressure to remove residual acetic acid. 4-Amino-2-(2,2,2-trifluoroethoxy)phenylacetic acid hydrochloride was obtained as a colorless gum (HPLC retention time = 4.2 min (method A)).

Step 7. Into a stirred solution of 4-amino-2-(2,2,2-trifluoroethoxy)phenylacetic acid hydrochloride (0.95 g, 3.5 mmol) from Step 6 above in MeOH (25 mL) at 0°C was bubbled HCl gas for 10 min. The resulting solution was warmed to ambient temperature and stirred for 14 h. The solvent was removed under reduced pressure to give methyl 4-amino-2-(2,2,2-trifluoroethoxy)phenylacetate hydrochloride as a solid (HPLC retention time = 5.6 min (method A)).

Step 8. To a solution of methyl 4-amino-2-(2,2,2-trifluoroethoxy)phenylacetate hydrochloride (1.0 g, 3.5 mmol) from Step 7 above in DMF (20 mL) was added di-tert-butyl-dicarbonate (0.85 g, 3.9 mmol) and DIEA (1.2 mL, 7.0 mmol). The solution was stirread at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (50 mL). The organic phase was separated, washed with water (25 mL), saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 20% EtOAc:hexanes as eluant. Methyl 4-(tert-butyloxycarbonylamino)-2-(2,2,2-trifluoroethoxy)phenylacetate was obtained as a colorless gum (TLC R_f = 0.40 (20% EtOAc:hexanes); HPLC retention time = 10.3 min (method A)).

Step 9. To a stirred solution of methyl 4-(tert-butyloxycarbonylamino)-2-(2,2,2-trifluoroethoxy)phenylacetate (0.90 g, 2.5 mmol) in MeOH (15 mL) was added aqueous NaOH (2.5 mL of a 3 N solution, 7.5 mmol). The mixture was refluxed for 1 h. The solvents were removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated, washed with water (25 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 4-(tert-butyloxycarbonylamino)-2-(2,2,2-trifluoroethoxy)-phenylacetic acid as an amorphous solid (HPLC retention time = 8.8 min (method A)).

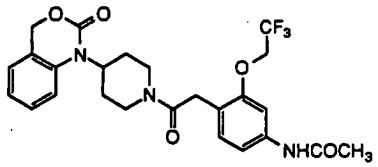
Step 10. To a stirred solution of 4-(tert-butyloxycarbonylamino)-2-(2,2,2-trifluoroethoxy)phenylacetic acid (0.20 g, 0.59 mmol) from Step 9 above in DMF (10 mL) was added 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.16 g, 0.59 mmol) from Step 4 of Example 1, HOBT (0.09 g, 0.6 mmol), EDC (0.15 g, 0.90 mmol), and DIEA (0.15 mL, 0.90 mmol). The solution was stirred at ambient temperature for 14 h during which time a precipitate had formed. The mixture was cooled, filtered, and the solid was washed with EtOAc and dried under reduced pressure to give 1-(1-(2-(2,2,2-trifluoroethoxy)-4-(tert-butyloxycarbonylamino)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as an amorphous solid (HPLC retention time = 10.4 min (method A); TLC R_f = 0.50 (3:1 EtOAc:hexanes).

Step 11. Into a stirred solution of 1-(1-(2-(2,2,2-trifluoroethoxy)-4-(tert-butyloxycarbonylamino)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.23 g, 0.41 mmol) from Step 10 above in EtOAc (75 mL) at 0°C was bubbled HCl gas for 15 min. The resulting suspension was stirred at 0°C for 45 min. Excess HCl was removed by bubbling argon though the mixture for 15 min. Ether (75 mL) was added and the cold suspension was filtered. The solids were washed with additional ether and dried under reduced pressure for 18 h to give the hydrochloride salt of the title compound as an amorphous white powder.
HPLC retention time = 7.3 min (method A)
TLC R_f = 0.4 (95:5 CH_2Cl_2:MeOH)
FAB MS: m/z = 464 ($M^+ + H$)
combustion analysis: $C_{23}H_{24}F_3N_3O_4 \cdot 1.0\ HCl, 0.35\ H_2O$

Calculated	C, 54.61; H, 5.12; N, 8.31
Found	C, 54.64; H, 5.20; N, 8.31

EXAMPLE 22

1-(1-(2-(2,2,2-trifluoroethoxy)-4-acetylaminophenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



To a stirred solution of the hydrochloride salt of 1-(1-(2-(2,2,2-trifluoroethoxy)-4-aminophenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.10 g, 0.20 mmol) from Example 21 above in CH_2Cl_2 (3 mL) at 0°C was added acetyl chloride (0.017 mL, 0.22 mmol) and TEA (0.063 mL, 0.45 mmol). The mixture was stirred at 0°C for 30 min and then at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using a water-acetonitrile gradient containing 0.1% TFA. The product-containing fractions were lyophilized to give the TFA salt of the title compound as an amorphous solid.

HPLC retention time = 8.4 min (method A)

TLC R_f = 0.4 (95:5 CH_2Cl_2:MeOH)

FAB MS: m/z = 506 (M^+ + H)

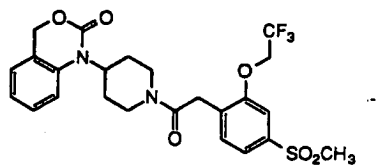
combustion analysis: $C_{25}H_{26}F_3N_3O_5$ •0.8 TFA

Calculated C, 53.54; H, 4.53; N, 7.04

Found C, 53.26; H, 4.58; N, 7.09

EXAMPLE 23

1-(1-(2-(2,2,2-trifluoroethoxy)-4-methylsulfonylphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 2-hydroxy-4-fluoro-acetophenone (10 g, 65 mmol) in DMF (300 mL) at 0°C was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (25 g, 120 mmol) and Cs_2CO_3 (39 g, 120 mmol). The mixture was stirred at 0°C for 2 h and then at ambient temperature for 14 h. EtOAc (300 mL) was added and the solid was removed by filtration. The filtrate solvents were removed under reduced pressure and the residue was partitioned between EtOAc (250 mL) and saturated aqueous $NaHCO_3$ (2 x 100 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 5% EtOAc:hexanes as eluant to give 2-(2,2,2-trifluoroethoxy)-4-fluoroacetophenone as a colorless oil (HPLC retention time = 8.8 min (method A); TLC Rf = 0.55 (20% EtOAc:hexanes)).

Step 2. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-fluoroacetophenone (0.40 g, 1.7 mmol) from Step 1 above in DMF (6 mL) was added sodium thiomethoxide (0.18 g, 2.6 mmol). The mixture was stirred at ambient temperature for 14 h, diluted with EtOAc (10 mL), filtered and the solvents were removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and water (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 2-(2,2,2-trifluoroethoxy)-4-thiomethoxyacetophenone as an oil (HPLC retention time = 9.6 min (method A)).

Step 3. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-thiomethoxyacetophenone (0.31 g, 1.2 mmol) from Step 2 above in MeOH (6 mL) was added trimethyl orthoformate (0.38 mL, 0.35 mmol) and thallium nitrate trihydrate (0.52 g, 1.2 mmol). The mixture was stirred at ambient temperature for 14 h. The precipitate which had formed was removed by filtration and the filtrate solvents were removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. HPLC and TLC analysis showed a three component mixture which was assumed to consist of methyl 2-(2,2,2-trifluoroethoxy)-4-

thiomethoxyphenylacetate and the sulfoxide and sulfone derivatives (HPLC retention time = 6.7 min, 9.3 min, 9.8 min (method A)).

Step 4. The mixture from Step 3 above (0.32 g, 1.1 mmol) was dissolved in THF (5 mL) and water (1 mL) and $LiOH \cdot H_2O$ was added (0.50 g, 1.2 mmol). The mixture was stirred at ambient temperature for 14 h, acidified to pH 2 with 5 N aqueous HCl, and the solvents were removed under reduced pressure. The resulting three component mixture was assumed to consist of 2-(2,2,2-trifluoroethoxy)-4-thiomethoxyphenylacetic acid and the sulfoxide and sulfone derivatives (HPLC retention time = 5.2 min, 7.8 min, 8.2 min (method A)).

Step 5. To a stirred solution of the three component mixture (0.30 g, 1.1 mmol) from Step 4 above and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.32 g, 1.2 mmol) from Step 4 of Example 1 in DMF (5 mL) was added HOBT (0.20 g, 1.2 mmol), EDC (0.31 g, 1.5 mmol), and DIEA (0.3 mL, 1.7 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The resulting three component mixture was assumed to consist of 1-(1-(2-(2,2,2-trifluoroethoxy)-4-thiomethoxy-phenyl-acetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one and the sulfoxide and sulfone derivatives (HPLC retention time = 7.8 min, 9.4 min, 9.9 min (method A)).

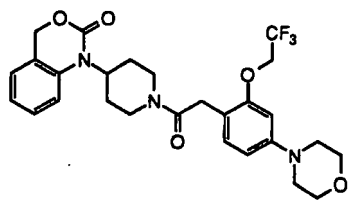
Step 6. The three component mixture (0.54 g, 1.1 mmol) from Step 5 above was dissolved in CH_2Cl_2 (5 mL) and MCPBA (0.19 g of a 50% by weight mixture, 2.2 mmol) was added. The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 97:3 CH_2Cl_2:MeOH as eluant. The product-

containing fractions were evaporated under reduced pressure to give the title compound as an amorphous solid.
HPLC retention time = 8.4 min (method A)
TLC R_f = 0.9 (90:10 CH_2Cl_2:MeOH)
FAB MS: m/z = 527 ($M^+ + H$)
combustion analysis: $C_{24}H_{25}F_3N_2O_6S \cdot 0.4\ H_2O$, 0.23 CH_2Cl_2

Calculated	C, 43.32; H, 4.20; N, 3.84
Found	C, 43.14; H, 3.83; N, 4.11

EXAMPLE 24

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(4-morpholinyl)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-fluoroacetophenone (0.40 g, 1.4 mmol) from Step 1 of Example 23 in DMF (10 mL) was added morpholine (0.44 mL, 5.1 mmol) and Cs_2CO_3 (1.1 g, 3.4 mmol). The mixture was heated to 50°C and stirred for 24 h. The solids were removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water. The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 10-50% EtOAc:hexanes to give 2-(2,2,2-trifluoro-ethoxy)-4-(4-morpholinyl)acetophenone as an amorphous solid (HPLC retention time = 8.1 min (method A)).

Step 2. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-(4-morpholinyl)acetophenone (0.225 g, 0.74 mmol)) from Step 1 above in MeOH (4 mL) was added trimethyl orthoformate (0.244 mL, 2.2 mmol) and thallium trinitrate trihydrate (0.33 g, 0.74 mmol). The mixture was stirred at ambient temperature for 14 h. The precipitate that had formed was removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give methyl 2-(2,2,2-trifluoro-ethoxy)-4-(4-

morpholinyl)phenylacetate as an oil (HPLC retention time = 7.5 min (method A)).

Step 3. To a stirred solution of methyl 2-(2,2,2-trifluoro-ethoxy)-4-(4-morpholinyl)phenylacetate (0.22 g, 0.67 mmol) from Step 2 above in THF (2 mL) and water (0.5 mL) was added $LiOH \cdot H_2O$ (0.056 g, 1.3 mmol). The mixture was stirred at ambient temperature for14 h. The solution was adjusted to pH 3 by the addition of 5 N aqueous HCl and the solvents were removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using a gradient elution of 0-50% MeOH:CH_2Cl_2 as eluant. 2-(2,2,2-Trifluoroethoxy)-4-(4-morpholinyl)phenylacetic acid was obtained as a gum (HPLC retention time = 5.8 min (method A)).

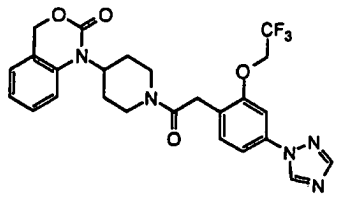
Step 4. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-(4-morpholinyl)phenylacetic acid (0.075 g, 0.24 mmol) from Step 3 above and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.071 g, 0.26 mmol) from Step 4 of Example 1 in DMF (2 mL) was added HOBT (0.045 g, 0.29 mmol), EDC (0.10 g, 0.5 mmol), and DIEA (0.085 mL, 0.5 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (10 mL), and saturated aqueous $NaHCO_3$ (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 98:2:0.1 CH_2Cl_2:MeOH:NH_4OH as eluant. The product was lyophilized from CH_3CN:H_2O to give the title compound as an amorphous solid.

HPLC retention time = 8.0 min (method A)
TLC R_f = 0.5 (95:5 CH_2Cl_2:MeOH)
FAB MS: m/z = 534 ($M^+ + H$)
combustion analysis: $C_{27}H_{30}F_3N_3O_5 \cdot 0.25\ H_2O$, 0.1 CH_3CN

Calculated	C, 60.25; H, 5.73; N, 8.01
Found	C, 60.29; H, 5.66; N, 8.06

EXAMPLE 25

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-triazolyl)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-fluoroacetophenone (0.40 g, 1.7 mmol) from Step 1 of Example 23 in DMF (10 mL) was added 1,2,4-triazole (0.18 g, 2.5 mmol) and Cs_2CO_3 (1.1 g, 3.4 mmol). The mixture was heated to 50°C and stirred for 24 h. The solids were removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water. The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 10-40% EtOAc:hexanes to give 2-(2,2,2-trifluoroethoxy)-4-(1-triazolyl)acetophenone as an amorphous solid (HPLC retention time = 7.6 min (method A)).

Step 2. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-(1-triazolyl)acetophenone (0.45 g, 1.6 mmol)) from Step 1 above in MeOH (8 mL) was added trimethyl orthoformate (0.52 mL, 4.8 mmol) and thallium trinitrate trihydrate (0.71 g, 1.6 mmol). The mixture was stirred at ambient temperature for 14 h. The precipitate that had formed was removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was partitioned between EtOAc (75 mL) and saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give methyl 2-(2,2,2-trifluoroethoxy)-4-(1-triazolyl)phenylacetate as an oil (HPLC retention time = 7.6 min (method A)).

Step 3. To a stirred solution of methyl 2-(2,2,2-trifluoroethoxy)-4-(1-triazolyl)phenylacetate (0.54 g, 1.7 mmol) from Step 2 above in THF (10 mL) and water (2.5 mL) was added $LiOH \cdot H_2O$ (0.11 g, 2.6 mmol). The mixture was stirred at ambient temperature for 14 h. The solution was adjusted to pH 2 by the addition of 5 N aqueous HCl and the solvents were removed under reduced pressure to give 2-(2,2,2-trifluoroethoxy)-4-(1-triazolyl)phenylacetic acid was obtained as a gum (HPLC retention time = 6.0 min (method A)).

Step 4. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-(1-triazolyl)phenylacetic acid (0.10 g, 0.33 mmol) from Step 3 above and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.09 g, 0.35 mmol) from Step 4 of Example 1 in DMF (2 mL) was added HOBT (0.06 g, 0.35 mmol), EDC (0.10 g, 0.5 mmol), and DIEA (0.09 mL, 0.5 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (10 mL), and saturated aqueous $NaHCO_3$ (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 98:2:0.1 CH_2Cl_2:MeOH:NH_4OH as eluant. The title compound as an amorphous solid.

HPLC retention time = 8.3 min (method A)

TLC R_f = 0.8 (90:10 CH_2Cl_2:MeOH)

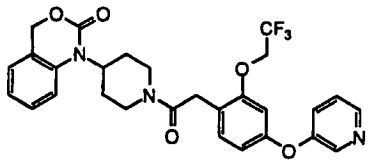
FAB MS: m/z = 516 ($M^+ + H$)

combustion analysis: $C_{25}H_{24}F_3N_5O_4 \cdot 0.1\ CH_2Cl_2$

Calculated	C, 57.18; H, 4.64; N, 13.26
Found	C, 57.29; H, 4.54; N, 13.46

EXAMPLE 26

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(3-pyridyloxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-fluoroacetophenone (0.40 g, 1.7 mmol) from Step 1 of Example 23 in DMF (10 mL) was added 3-hydroxypyridine (0.24 g, 2.5 mmol) and Cs_2CO_3 (1.1 g, 3.4 mmol). The mixture was heated to 50°C and stirred for 14 h. The solids were removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water. The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 2-(2,2,2-trifluoroethoxy)-4-(3-pyridyloxy)acetophenone as an amorphous solid (HPLC retention time = 6.6 min (method A)).

Step 2. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-(3-pyridyloxy)acetophenone (0.48 g, 1.5 mmol)) from Step 1 above in MeOH (8 mL) was added trimethyl orthoformate (0.50 mL, 4.5 mmol) and thallium trinitrate trihydrate (0.68 g, 1.5 mmol). The mixture was stirred at ambient temperature for 14 h. The precipitate that had formed was removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was partitioned between EtOAc (75 mL) and saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give methyl 2-(2,2,2-trifluoroethoxy)-4-(3-pyridyloxy)phenylacetate as an oil (HPLC retention time = 6.6 min (method A)).

Step 3. To a stirred solution of methyl 2-(2,2,2-trifluoroethoxy)-4-(3-pyridyloxy)phenylacetate (0.45 g, 1.3 mmol) from Step 2 above in THF (4 mL) and water (1 mL) was added $LiOH \cdot H_2O$ (0.065 g, 1.5 mmol). The mixture was stirred at ambient temperature for 14 h. The solution was adjusted to pH 3 by the addition of 5 N aqueous HCl and the solvents were removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 0-20% MeOH:CH_2Cl_2 to give 2-(2,2,2-trifluoro-ethoxy)-4-(3-pyridyloxy)-phenylacetic acid as a gum (HPLC retention time = 5.4 min (method A)).

Step 4. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-(3-pyridyloxy)phenylacetic acid (0.10 g, 0.31 mmol) from Step 3 above and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.09 g, 0.35 mmol) from Step 4 of Example 1 in DMF (2 mL) was added HOBT (0.06 g, 0.35 mmol), EDC (0.10 g, 0.5 mmol), and DIEA (0.09 mL, 0.5 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 98:2:0.1 CH_2Cl_2:MeOH:NH_4OH as eluant. Lyophilization from CH_3CN:H_2O gave the title compound as an amorphous solid.

HPLC retention time = 7.5 min (method A)

TLC R_f = 0.8 (90:10 CH_2Cl_2:MeOH)

FAB MS: m/z = 542 ($M^+ + H$)

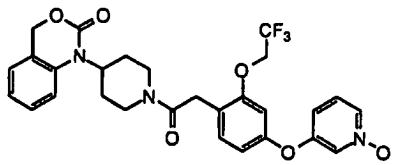
combustion analysis: $C_{28}H_{26}F_3N_3O_5 \cdot 0.1\ CH_3CN, 0.3\ H_2O$

Calculated C, 61.46; H, 4.92; N, 7.88

Found C, 61.45; H, 4.83; N, 7.91

EXAMPLE 27

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(3-(1-oxo)pyridyloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



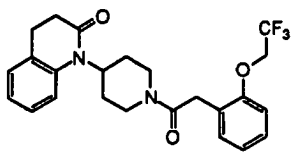
To a stirred solution of 1-(1-(2-(2,2,2-trifluoroethoxy)-4-(3-pyridyloxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.050 g, 0.09 mmol) from Example 27 in CH_2Cl_2 (0.5 mL) was added MCPBA (0.055 g of a 50% by weight mixture, 0.18 mmol). The mixture was stirred at ambient temperature for 14 h. The mixture was diluted with CH_2Cl_2 and extracted with 2 N aqueous NaOH. The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give the title compound as an amorphous solid.

HPLC retention time = 7.0 min (method A)
TLC R_f = 0.7 (90:10 CH_2Cl_2:MeOH)
FAB MS: m/z = 558 ($M^+ + H$)
combustion analysis: $C_{28}H_{26}F_3N_3O_6 \cdot 1.1\ CH_2Cl_2$

Calculated	C, 53.43; H, 4.35; N, 6.41
Found	C, 53.48; H, 4.20; N, 6.32

EXAMPLE 28

1-(1-(2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one



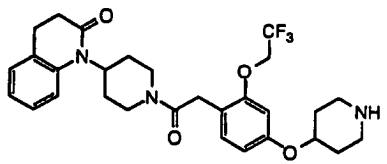
To a stirred solution of 2-(2,2,2-trifluoroethoxyphenyl-acetic acid (0.20 g, 0.90 mmol) from Step 2 of Example 16 and 1-(piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one prepared by the method of Ogawa, et al., J. Med. Chem. (1993), vol. 36, pp. 2011-2017) (0.24 g, 0.90 mmol) in DMF (15 mL) was added HOBT (0.15 g, 1.0 mmol), EDC (0.44 g, 1.5 mmol), and DIEA (0.3 mL, 1.7 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 97:2 CH_2Cl_2:MeOH as eluant to give the title compound as an amorphous solid.

HPLC retention time = 9.3 min (method A)
TLC R_f = 0.25 (97:2 CH_2Cl_2:MeOH)
FAB MS: m/z = 447 ($M^+ + H$)
combustion analysis: $C_{24}H_{25}F_3N_2O_3 \cdot 0.1\ CH_2Cl_2$, 0.05 MeOH

Calculated	C, 63.53; H, 5.61; N, 6.14
Found	C, 63.47; H, 5.60; N, 6.40

EXAMPLE 29

1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one



Step 1. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetic acid from Step 8 of Example 1 and 1-(piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one prepared by the method of Ogawa, et al., J. Med. Chem. (1993), vol. 36, pp. 2011-2017) in DMF was added HOBT, EDC, and DIEA. The solution was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (75 mL). The organic phase was separated and washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (75 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using EtOAc as eluant. The product-containing fractions were evaporated under reduced pressure to give 1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-3,4-dihydro-quinolin-2(1H)-one as an amorphous solid (HPLC retention time = 10.8 min (method A); TLC Rf = 0.7 (EtOAc)).

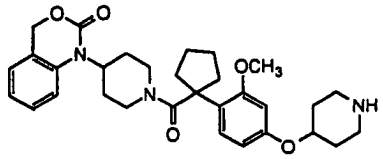
Step 2. Into a stirred solution of (N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one (1.2 g, 1.8 mmol) from Step 1 above in EtOAc (75 mL) at 0°C was bubbled HCl gas for 15 min. The resulting suspension was stirred at 0°C for 45 min. Excess HCl was removed by bubbling argon though the mixture for 15 min. Ether (150 mL) was

added and the cold suspension was filtered. The solids were washed with additional ether and then dried under reduced pressure for 18 h to give the hydrochloride salt of the title compound as an amorphous white powder.

HPLC retention time = 7.5 min (method A)
TLC R_f = 0.44 (90:10:0.5 CH_2Cl_2:MeOH:NH_4OH)
FAB MS: m/z = 546 ($M^+ + H$)
combustion analysis: $C_{28}H_{32}F_3N_3O_5 \cdot 1.0$ HCl, 0.75 H_2O
Calculated C, 58.48; H, 6.18; N, 7.06
Found C, 58.45; H, 6.22; N, 7.05

EXAMPLE 30

1-(1-(1-(4-(4-piperidinyloxy)-2-methoxyphenyl)cyclopentylcarbonyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred, 0°C solution of triphenylphosphine (57.2 g, 0.218 mol) and 2,4-dihydroxybenzoic acid methyl ester (29.2 g, 0.174 mol) in dry THF (200 mL) was added a solution of N-t-butyloxy-4-piperidinol (35 g, 0.174 mol) and diethylazodicarboxylate (32.9 mL, 0.209 mol) in dry THF (150 mL) dropwise over a period of 2 h. The resulting solution was slowly warmed to ambient temperature over 6 h and stirred for an additional 16 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (500 mL) and washed with 10% aqueous Na_2CO_3 (3x 250 mL), water (150 mL), and brine (150 mL). The EtOAc layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica

gel column chromatography using a gradient elution of 10-25% EtOAc-hexane. 4-(N-t-Butoxycarbonyl-4-piperi-dinyloxy)-2-hydroxybenzoic acid methyl ester was obtained as a waxy solid.

Step 2. 4-(N-t-Butoxycarbonyl-4-piperidinyloxy)-2-hydroxy-benzoic acid methyl ester (10 g, 28 mmol) from Step 1 was dissolved in DMF (100 mL) and cooled to 0°C. To the stirred solution was added iodomethane (6.1 g, 43 mmol) and Cs_2CO_3 (10 g, 31 mmol). The mixture was stirred at 0°C for 1 h and then at ambient temperature for 12 h. The solids were removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 20-40% EtOAc-hexane. 4-(N-t-Butoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoic acid methyl ester was obtained as an oil.

Step 3. 4-(N-t-Butoxycarbonyl-4-piperidinyloxy)-2-methoxy-benzoic acid methyl ester (1.0 g, 2.7 mmol) from Step 2 was refluxed in EtOH (15 mL) conatining aqueous NaOH (5.5 mL of a 1.0 N solution). The solvents were removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (50 mL). The organic phase was washed with water (25 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 4-(N-t-Butoxycarbonyl-4-piperidinyloxy)-2-methoxy-benzoic acid as an amorphous solid.

Step 4. To a solution of 2-methoxy-(N-t-butyloxycarbonyl-4-piperidyloxy)benzoic acid (3.2 g; 9.1 mmol) from Step 3 above in THF was added thionyl chloride (1 mL; 13.7 mmol) and pyridine (2 drops) while under a nitrogen atmosphere. The solution was stirred for 4 hours and then concentrated under reduced pressure to dryness. The residue was suspended in ether and filtered, and the filtrate was concentrated to dryness to yield 2-methoxy-(N-t-butyloxycarbonyl-4-piperidyloxy)benzoyl chloride.

Step 5. A two phase mixture of ether (66 mL) and 40% aqueous potassium hydroxide (20 mL) was cooled to 0°C and N-nitroso-methylurea (6.6 g) was added portionwise over 30 minutes. The resulting yellow diazomethane/ether solution was decanted and dried over potassium hydroxide. The diazomethane/ether solution was

decanted and cooled to 0°C. At this point, a solution of 2-methoxy-(N-t-butyloxycarbonyl-4-piperidyloxy)benzoyl chloride from Step 4 above in THF was added dropwise to the diazomethane/ether solution. The resulting bronze solution was warmed to ambient temperature and stirred for 3 hours. Nitrogen was bubbled through the reaction mixture for 1 hour to remove excess diazomethane and the solution was concentrated under reduced pressure to dryness. The residue was purified by pressurized silica gel column chromatography (elute with 6:94 ether:methylene chloride) to yield 2-methoxy-(N-t-butyloxy-carbonyl-4-piperidyloxy)phenyldiazomethyl ketone.

Step 6. A solution of 2-methoxy-(N-t-butyloxycarbonyl-4-piperidyloxy)phenyldiazomethyl ketone (930 mg; 2.48 mmol) from Step 6 above in dry methanol (7 mL) was refluxed and a solution of freshly prepared silver benzoate (100 mg) in triethylamine (1 mL) was added portionwise over 45 minutes. The solution was refluxed for an additional 30 minutes, then cooled and filtered. The filtrate was concentrated to dryness and the crude oil was purified by pressurized silica gel column chromatography (elute with 5:95 methanol:methylene chloride) to yield methyl-2-methoxy-(N-t-butyloxycarbonyl-4-piperidyloxy)phenyl acetate.

Step 7. To a stirred solution of methyl-2-methoxy-(N-t-butyloxycarbonyl-4-piperidyloxy)phenylacetate (0.50 g, 1.3 mmol) from Step 6 in THF (15 mL) at -78°C was added lithium hexamethyldisilazide (2.9 mL of a 1.0 M solution in THF). The mixture was stirred at -78°C for 1 h and 1,4-diiodobutane (0.40 g, 1.3 mmol) was added. The mixture was stirred at -78°C for 60 min and then at ambient temperature for 14 h. The mixture was cooled to -78°C and more lithium hexamethyldisilazide (1.3 mmol of a 1.0 M solution in THF) was added. The mixture was warmed to ambient temperature ans stirred for 24 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and water (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel coulmn chromatography using 15% EtOAc:hexanes as eluant to give 1-(1-(1-(4-(N-Boc-4-piperidinyloxy)-2-methoxyphenyl)cyclopentylcarboxylic acid

methyl ester as an oil (HPLC retention time = 11.6 min (method A); TLC Rf = 0.2 (4:1 hexanes:EtOAc)).

Step 8. To a solution of 1-(1-(1-(4-(N-Boc-4-piperidinyloxy)-2-methoxyphenyl)cyclopentylcarboxylic acid methyl ester (0.20 g, 0.46 mmol) from Step 7 above in MeOH (5 mL) was added aqueous NaOH (1.15 mL of a 2.0 N solution, 2.3 mmol). The mixture was refluxed for 5 days. The mixture was acidified to pH 2 by the addition of 2 N aqueous HCl and the solvent was removed under reduced pressure. The residue was suspended in DMF (5 mL) and to the mixture was added DIEA (0.17 mL, 1.0 mmol) and di-tert-butyldicarbonate (0.10 g, 0.46 mmol) were added and the mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was washed with water (25 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 1-(1-(1-(4-(N-Boc-4-piperidinyloxy)-2-methoxyphenyl)cyclopentylcarboxylic acid as an amorphous solid (HPLC retention time = 10.0 min (method A)).

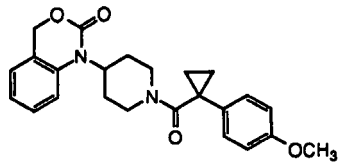
Step 9. To a solution of 1-(1-(1-(4-(N-Boc-4-piperidinyloxy)-2-methoxyphenyl)cyclopentylcarboxylic acid (0.15 g, 0.36 mmol) from Step 8 above in DMF (10 mL) was added 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.10 g, 0.36 mmol) from Step 4 of Example 1, BOP (0.18 g, 0.40 mmol), and DIEA (0.125 mL, 0.72 mmol). The mixture was stirred for 3 h at ambient temperature and then at 60°C for 48 h. The solvent was removed under reduced pressure and the reisude was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was washed with water (10 mL), saturated aqueous $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using EtOAc as eluant. The product was further purified by preparative reverse phase HPLC using a water-acetonitrile gradient containing 0.1% TFA. Lyophilization of the combined product-containing fractions gave 1-(1-(1-(4-(N-Boc-4-piperidinyloxy)-2-methoxyphenyl)cyclopentyl-carbonyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as an amorphous powder

(HPLC retention time = 12.5 min (method A); TLC Rf = 0.29 (4:1 EtOAc:hexanes)).

Step 10. Into a solution of 1-(1-(1-(4-(N-Boc-4-piperidinyloxy)-2-methoxyphenyl)cyclopentylcarbonyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.15 g, 0.24 mmol) from Step 9 above in EtOAc (10 mL) at 0°C was bubbled HCl gas for 10 min. The solution was warmed to ambient temperature and stirred for 1 h. The solvent was removed under reduced pressure to give the title compound as an amorphous solid.
HPLC retention time = 6.9 min (method A)
TLC R_f = 0.32 (90:10:1 CH_2Cl_2:MeOH:NH4OH)
FAB MS: m/z = 534 ($M^+ + H$)

EXAMPLE 31

1-(1-(1-(4-methoxyphenyl)cyclopropylcarbonyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one

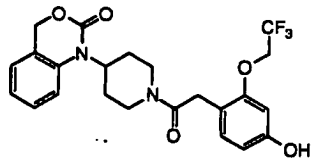


To a stirred solution of 1-(4-methoxyphenyl)cyclopropane-1-carboxylic acid (0.071 g, 0.37 mmol) and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.10 g, 0.37 mmol) from Step 4 of Example 1 in DMF (3 mL) was added HOBT (0.06 g, 0.4 mmol), EDC (0.10 g, 0.5 mmol), and DIEA (0.085 mL, 0.5 mmol). The solution was stirred at ambient temperature for 24 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (10 mL), and saturated aqueous $NaHCO_3$ (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using EtOAc as eluant. The product was lyophilized from CH_3CN:H_2O to give the title compound as an amorphous solid.

HPLC retention time = 8.9 min (method A)
TLC R_f = 0.5 (95:5 CH_2Cl_2:MeOH)
FAB MS: m/z = 407 ($M^+ + H$)
combustion analysis: $C_{24}H_{26}N_2O_4 \cdot 0.3\ H_2O$
Calculated C, 69.98; H, 6.51; N, 6.80
Found C, 69.98; H, 6.27; N, 6.89

EXAMPLE 32

1-(1-(2-(2,2,2-trifluoroethoxy)-4-hydroxyphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 2,2,2-trifluoroethanol (3.0 g, 34 mmol) in THF (20 mL) at 0°C was added potassium tert-butoxide (32 mL of a 1.0 M solution in THF, 32 mmol). The solution was stirred for 10 min, cooled to -78°C, and 2,4-difluoroacetophenone (5.0 g, 32 mmol) was added. The resulting solution was stirred at -78°C for 10 min, at 0°C for 3 h, and then at ambient temperature for 12 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (150 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. 4-Fluoro-2-(2,2,2-trifluoroethoxy)acetophenone was obtained as a solid by crystallization from ether (HPLC retention time = 8.9 min (method A); TLC R_f = 0.60 (13% EtOAc:hexanes)).

Step 2. To a stirred solution of benzyl alcohol (4.0 g, 37 mmol) in THF (40 mL) at 0°C was added potassium tert-butoxide (35 mL of a 1.0 M solution in THF, 35 mmol). The solution was stirred for 10 min and 4-fluoro-2-(2,2,2-trifluoroethoxy)acetophenone (6.4 g, 28 mmol) from Step 1 above was added. The solution was stirred at 0°C for 1 h and at ambient temperature for 4 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (200 mL) and saturated aqueous $NaHCO_3$ (150 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 10% EtOAc:hexanes as eluant. The major component was isolated and crystallized from 1:10 ether:hexanes to give 4-benzyloxy-2-(2,2,2-trifluoroethoxy)acetophenone as a colorless solid (HPLC retention time = 10.8 min (method A); TLC R_f = 0.46 (15% EtOAc:hexanes)).

Step 3. To a stirred solution of 4-benzyloxy-2-(2,2,2-trifluoroethoxy)acetophenone (3.07 g, 9.46 mmol) from Step 2 above in MeOH (75 mL) was added trimethyl orthoformate (3.1 mL, 2.8 mmol) and thallium trinitrate trihydrate (4.2 g, 9.5 mmol). The mixture was stirred at ambient temperature for 14 h. The solid was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered,

and the solvent was removed under reduced pressure to give methyl 4-benzyloxy-2-(2,2,2-trifluoroethoxy)phenylacetate as an oil (HPLC retention time = 28.6 min (method D)).

Step 4. To a stirred solution of methyl 4-benzyloxy-2-(2,2,2-trifluoroethoxy)phenylacetate from Step 3 in MeOH was added palladium black (250 mg). The mixture was stirred under an atmosphere of hydrogen gas (1 atm) for 3 h. The hydrogen was removed by bubbling argon through the mixture for 10 min, and the catalyst was removed by filtration. The filtrate solvents were removed inder reduced pressure and the residue was purified by pressurized silica gel column chromatography using 1:3 EtOAc:hexanes as eluant to give methyl 4-hydroxy-2-(2,2,2-trifluoroethoxy)phenylacetate as a solid (HPLC retention time = 18.1 min (method D)).

Step 5. To a stirred solution of methyl 4-hydroxy-2-(2,2,2-trifluoroethoxy)phenylacetate (1.3 g, 4.8 mmol) from Step 4 above in THF (15 mL) was added water (3 mL) and LiOH (0.62 g, 15 mmol). The mixture was stirred at ambient temperature for 6 h and the solvents were removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and aqueous citric acid. The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 4-hydroxy-2-(2,2,2-trifluoroethoxy)phenylacetic acid as an amorphous solid (HPLC retention time = 13.2 min (method D)).

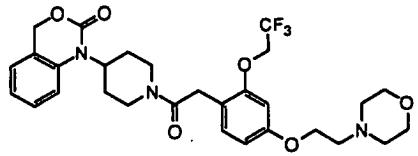
Step 6. To a stirred solution of 4-hydroxy-2-(2,2,2-trifluoroethoxy)phenylacetic acid from Step 5 above (1.1 g, 4.6 mmol) and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (1.3 g, 4.8 mmol) from Step 4 of Example 1 in DMF was added HOBT (0.70 g, 4.6 mmol), EDC (1.3 g, 6.9 mmol), and DIEA (1.4 mL, 8.0 mmol). The solution was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (75 mL). The organic phase was separated and washed with H_2O (50 mL), and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by preparative reverse-phase HPLC using a H_2O:CH_3CN gradient

containing 0.1% TFA. The product-containing fractions were lyophilized to give the title compound as an amorphous solid.
HPLC retention time = 20.5 min (method D)
TLC R_f = 0.44 (95:5 CH_2Cl_2:MeOH)
FAB MS: m/z = 465 ($M^+ + H$)
combustion analysis: $C_{23}H_{23}F_3N_2O_5$ •0.1 TFA, 0.05 CH_3CN

Calculated	C, 58.11; H, 4.86; N, 5.94
Found	C, 57.99; H, 4.86; N, 5.97

EXAMPLE 33

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(2-(4-morpholinyl)ethoxy)phenyl-acetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



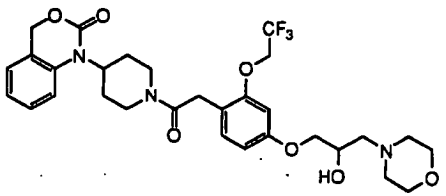
To a solution of 1-(1-(2-(2,2,2-trifluoroethoxy)-4-hydroxyphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.10 g, 0.22 mmol) from Example 32 in DMF (2 mL) was added 4-(2-chloroethyl)morpholine hydrochloride (0.061 g, 0.33 mmol) and Cs_2CO_3 (0.20 g, 0.60 mmol). The mixture was warmed to 40°C and stirred for 24 h. Additional 4-(2-chloroethyl)morpholine hydrochloride (0.061 g, 0.33 mmol) and Cs_2CO_3 (0.20 g, 0.60 mmol) were added and the mixture was stirred for 24 h at 40°C. The solids were removed by filtration and the filtrate solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPLC using a H_2O:CH_3CN gradient containing 0.1% TFA. The product-containing fractions were combined and lyophilized to give the TFA salt of the title compound as an amorphous powder.

HPLC retention time = 19 min (method D)
TLC R_f = 0.51 (95:5 CH_2Cl_2:MeOH)
FAB MS: m/z = 578 (M^+ + H)
combustion analysis: $C_{29}H_{34}F_3N_3O_6$ •1.6 TFA

Calculated	C, 50.88; H, 4.72; N, 5.53
Found	C, 50.96; H, 4.26; N, 5.36

EXAMPLE 34

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(3-(4-morpholinyl)-2-hydroxy-propyloxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of methyl 4-hydroxy-2-(2,2,2-trifluoroethoxy)phenylacetate (0.60 g, 2.4 mmol) from Step 4 of Example 32 in DMF (7 mL) was added epibromohydrin (0.50 g, 3.6 mmol) and Cs_2CO_3 (1.55 g, 4.8 mmol). The mixture was stirred at ambient temperature for 3 h. EtOAc was added (15 mL) and the solid was removed by filtration. The filtrate solvents were removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give methyl 4-(glycidyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetate as a pale yellow oil (HPLC retention time = 8.3 min (method A)).

Step 2. To a solution of methyl 4-(glycidyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetate (0.25 g, 0.81 mmol) from Step 1 above in MeOH (3 mL) was added morpholine (0.5 mL). The solution was kept at

ambient temperature for 12 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and water (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give methyl 4-(3-(1-morpholinyl)-2-hydroxypropyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetate as a pale yellow oil (HPLC retention time = 6.5 min (method A); TLC R_f = 0.55 (95:5 CH_2Cl_2:MeOH)).

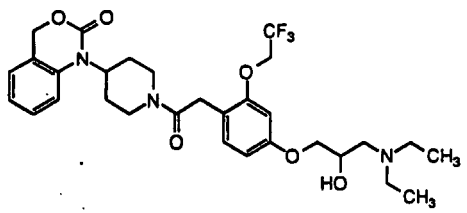
Step 3. To a solution of methyl 4-(3-(1-morpholinyl)-2-hydroxypropyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetate (0.26 g, 0.66 mmol) from Step 2 above in MeOH (3 mL) was added aqueous NaOH (1.5 mL of a 2.0 N solution, 3.0 mmol). The mixture was stirred at 70°C for 30 min. The solvent was removed under reduced pressure to give the sodium salt of 4-(3-(1-morpholinyl)-2-hydroxypropyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetic acid as an amorphous solid (HPLC retention time = 5.1 min (method A)).

Step 4. To a stirred solution of the sodium salt of 4-(3-(1-morpholinyl)-2-hydroxypropyloxy)-2-(2,2,2-trifluoroethoxy)phenyl-acetic acid (0.33 mmol) from Step 3 above, 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.10 g, 0.37 mmol) from Step 4 of Example 1 in DMF (1.5 mL) was added HOBT (0.05g, 0.33 mmol), EDC (0.125 g, 0.66 mmol), and DIEA (0.11 mL, 0.66 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (30 mL) and saturated aqueous $NaHCO_3$ (2 x 10 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 3% MeOH:CH_2Cl_2 as eluant. The product-containing fractions were evaporated under reduced pressure to give the title compound as an amorphous solid.
HPLC retention time = 7.6 min (method A)
TLC R_f = 0.30 (4:96 MeOH:CH_2Cl_2)
FAB MS: m/z = 608 (M^+ + H)
combustion analysis: $C_{30}H_{36}F_3N_3O_7$ •0.15 CH_2Cl_2

Calculated	C, 58.37; H, 5.90; N, 6.77
Found	C, 58.56; H, 5.92; N, 6.74

EXAMPLE 35

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(3-diethylamino-2-hydroxypropyloxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a solution of methyl 4-(glycidyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetate (0.25 g, 0.81 mmol) from Step 1 of Example 34 in MeOH (3 mL) was added diethylamine (0.5 mL). The solution was kept at ambient temperature for 12 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and water (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give methyl 4-(3-diethylamino-2-hydroxypropyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetate as a pale yellow oil (HPLC retention time = 6.9 min (method A); TLC R_f = 0.23 (95:5 CH_2Cl_2:MeOH)).

Step 2. To a solution of methyl 4-(3-diethylamino-2-hydroxypropyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetate (0.26 g, 0.66 mmol) from Step 2 above in MeOH (3 mL) was added aqueous NaOH (1.5 mL of a 2.0 N solution, 3.0 mmol). The mixture was stirred at 70°C for 30 min. The solvent was removed under reduced pressure to give the sodium salt of 4-(3-diethylamino-2-hydroxypropyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetic acid as an amorphous solid (HPLC retention time = 5.5 min (method A)).

Step 3. To a stirred solution of the sodium salt of 4-(3-diethylamino-2-hydroxypropyloxy)-2-(2,2,2-trifluoroethoxy)phenyl-acetic acid (0.33 mmol) from Step 2 above, 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.10 g, 0.37 mmol) from Step 4 of Example 1 in DMF (1.5 mL) was added HOBT (0.05g, 0.33 mmol), EDC (0.125 g, 0.66 mmol), and DIEA (0.11 mL, 0.66 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (30 mL) and saturated aqueous $NaHCO_3$ (2 x 10 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 3% MeOH:CH_2Cl_2 as eluant to give the title compound as an amorphous solid.

HPLC retention time = 7.9 min (method A)

TLC R_f = 0.45 (95:5:0.25 CH_2Cl_2:MeOH:NH_4OH)

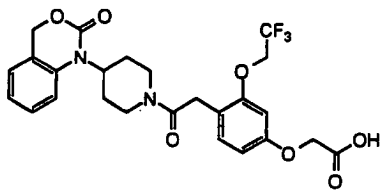
FAB MS: m/z = 594 ($M^+ + H$)

combustion analysis: $C_{30}H_{38}F_3N_3O_8 \cdot 0.55\ CH_2Cl_2$

Calculated	C, 57.30; H, 6.15; N, 6.56
Found	C, 57.30; H, 6.13; N, 6.62

EXAMPLE 36

1-(1-(2-(2,2,2-trifluoroethoxy)-4-carboxymethoxyphenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 1-(1-(2-(2,2,2-trifluoro-ethoxy)-4-hydroxyphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.54 g, 1.2 mmol) from Example 32 in DMF (10 mL) was added tert-butyl bromoacetate (0.51 mL, 3.6 mmol) and Cs_2CO_3 (0.48 g, 1.5 mmol). The mixture was stirred at ambient temperature for 18 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (10 mL) and water (50 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure to give 1-(1-(2-(2,2,2-trifluoro-ethoxy)-4-(tert-butyloxycarbonylmethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as a pale yellow oil (HPLC retention time = 27.3 min (method D)).

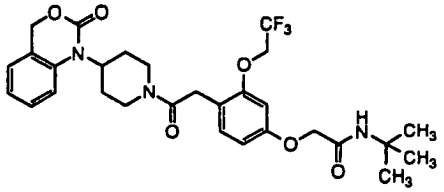
Step 2. To a solution of 1-(1-(2-(2,2,2-trifluoroethoxy)-4-(tert-butyloxycarbonylmethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.72 mg, 1.2 mmol) from Step 1 above in CH_2Cl_2 (20 mL) was added TFA (20 mL). After standing at ambient temperature for 1.5 h the solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using a H_2O:CH_3CN gradient containing 0.1% TFA. The product-containing fractions were combined and lyophilized to give the title compound as an amorphous powder.

HPLC retention time = 20.5 min (method D)
TLC R_f = 0.44 (95:5 CH_2Cl_2:MeOH)

FAB MS: m/z = 523 (M^+ + H)
combustion analysis: $C_{25}H_{25}F_3N_2O_7$ •0.55 TFA, 0.15 CH_3CN
Calculated C, 53.62; H, 4.43; N, 5.09
Found C, 53.56; H, 4.06; N, 5.08

EXAMPLE 37

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(tert-butylaminocarbonylmethoxy-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



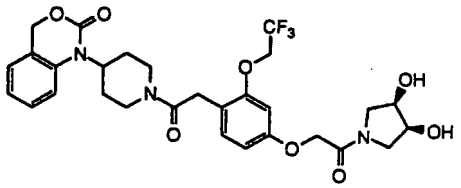
To a stirred solution of 1-(1-(2-(2,2,2-trifluoroethoxy)-4-carboxymethoxyphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.10 g, 0.19 mmol) from Example 36, tert-butylamine (0.037 mL, 0.40 mmol), and HOBT (0.03 g, 0.2 mmol) in DMF (1 mL) was added EDC (0.057 g, 0.3 mmol) and DIEA (0.07 mL, 0.4 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using a H_2O:CH_3CN gradient containing 0.1% TFA. The product-containing fractions were combined and lyophilized to give the title compound as an amorphous powder.

HPLC retention time = 26 min (method D)
TLC R_f = 0.57 (95:5 CH_2Cl_2:MeOH)
FAB MS: m/z = 578 (M^+ + H)
combustion analysis: $C_{29}H_{34}F_3N_3O_6$ •0.75 TFA
Calculated C, 55.24; H, 5.28; N, 6.34

Found C, 55.42; H, 4.92; N, 6.34

EXAMPLE 38

1-(1-(2-(2,2,2-trifluoroethoxy)-4-((3,4-dihydroxypyrrolidinyl)-carbonyl-methoxyphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one

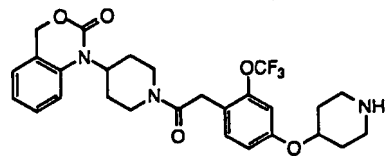


To a stirred solution of 1-(1-(2-(2,2,2-trifluoroethoxy)-4-carboxymethoxyphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.10 g, 0.19 mmol) from Example 36, cis-3,4-dihydroxy-pyrrolidine (0.041 g, 0.40 mmol), and HOBT (0.03 g, 0.2 mmol) in DMF (1 mL) was added EDC (0.057 g, 0.3 mmol) and DIEA (0.07 mL, 0.4 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using a H_2O:CH_3CN gradient containing 0.1% TFA. The product-containing fractions were combined and lyophilized to give the title compound as an amorphous powder.
HPLC retention time = 18.3 min (method D)
TLC R_f = 0.61 (90:10 CH_2Cl_2:MeOH)
FAB MS: m/z = 608 (M^+ + H)
combustion analysis: $C_{29}H_{32}F_3N_3O_8$ •0.75 TFA, 0.1 H_2O

Calculated C, 52,97; H, 4.81; N, 6.10
Found C, 52.95; H, 4.79; N, 6.22

EXAMPLE 39

1-(1-(2-trifluoromethoxy-4-(4-piperidinyloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of 4-bromo-2-(trifluoro-methoxy)iodobenzene (9.93 g, 28 mmol) in THF (150 mL) at -78°C was added tert-butyllithium (37 mL of a 1.5 M solution in pentane, 56 mmol) dropwise over a period of 20 min. The pale yellow solution was stirred at -78°C for 1.5 h when N-formylmorpholine (6.5 mL; 58 mmol) was added. The resulting solution was stirred at -78°C for 15 min and the cooling bath was removed. The mixture was stirred for an additional 1 h, when 0.25 M aqueous citric acid (100 mL) was added. The mixture was diluted with EtOAc (150 mL), the layers were separated, the organic phase was washed with brine (100 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified using pressurized silica gel column chromatography eluting with hexane to give 4-bromo-2-(trifluoro-methoxy)benzaldehyde as a colorless liquid (TLC R_f = 0.45 (hexanes)).

Step 2. To a stirred solution of 4-bromo-2-(trifluoro-methoxy)benzaldehyde (5.0 g, 19 mmol) from Step 1 above in EtOH (100 mL) at 0°C was added $NaBH_4$ (0.88 g, 23 mmol). The mixture was stirred for 1 h at 0°C, the cooling bath was removed, and the solution was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (150 mL) and saturated aqueous $NaHCO_3$ (75 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 5-10% EtOAc:hexanes. 4-Bromo-2-(trifluoromethoxy)benzyl alcohol was

obtained as an amorphous solid by evaporation from CH_2Cl_2 (TLC R_f = 0.25 (10% EtOAc:hexanes); HPLC retention time = 8.8 min (method A)).

Step 3. To a stirred solution of bromo-2-(trifluoromethoxy)benzyl alcohol (4.8 g, 18 mmol) in CH_2Cl_2 (100 mL) was added tert-butylchlorodimethylsilane (4.1 g, 27 mmol), triethylamine (3.8 mL, 27 mmol), and DMAP (1.2 g, 9.8 mmol). The mixture was stirred at ambient temperature for 24 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (150 mL) and 0.25 M aqueous citric acid (75 mL). The organic phase was washed with H_2O (50 mL), saturated aqueous $NaHCO_3$ (75 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using hexanes as eluant to give 4-bromo-1-(tert-butyldimethylsilyloxymethyl)-2-trifluoromethoxy-benzene as a colorless oil (TLC R_f = 0.60 (hexanes)).

Step 4. To a stirred solution of 4-bromo-1-(tert-butyl-dimethylsilyloxymethyl)-2-trifluoromethoxybenzene (5.5 g, 15 mmol) from Step 3 above in THF (100 mL) at -78°C was added n-butyllithium (6.6 mL of a 2.5 M solution in hexanes, 16.5 mmol) dropwise over a period of 10 min. The resulting pale yellow solution was stirred at -78°C for 30 min and trimethylborate (1.75 g, 17 mmol) was added. The resulting solution was stirred at -78°C for 5 min and then warmed to ambient temperature for 45 min. To the mixture was added acetic acid (0.90 mL, 15 mmol) and hydrogen peroxide (0.1.7 mL of a 30% solution in water, 17 mmol) and stirring was continued for 1 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (150 mL) and water (2 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 10% EtOAc:hexanes as eluant to give 4-hydroxy-1-(tert-butyldimethylsilyloxymethyl)-2-trifluoromethoxy-benzene as a colorless oil (TLC R_f = 0.40 (10% EtOAc:hexanes)).

Step 5. To a stirred solution of 4-hydroxy-1-(tert-butyl-dimethylsilyloxymethyl)-2-trifluoromethoxybenzene (3.2 g, 10 mmol)

from Step 4 above and triphenylphosphine (3.9 g, 15 mmol) in THF (50 mL) at 0°C was added a solution of N-tert-butyloxycarbonyl-4-piperidinol (3.0 g, 15 mmol) and DEAD (2.6 g, 15 mmol) in THF (25 mL) dropwise over a period of 1 h. The mixture was stirred at 0°C for 3h and then at ambient temperature for 12 h. The solvent was removed under reduced pressure and the residue was suspended in ether. The solid triphenylphosphine oxide was removed by filtration and the filtrate was purified by pressurized silica gel column chromatography using a gradient elution of 5-10% EtOAc:hexanes as eluant to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-1-(tert-butyldimethylsilyloxy-methyl)-2-trifluoromethoxybenzene as a colorless gum.

Step 6. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-1-(tert-butyldimethylsilyloxymethyl)-2-trifluoromethoxybenzene (3.5 g, 7.1 mmol) from Step 5 above in THF (50 mL) was added TBAF (8 mL of a 1.0 M solution in THF, 8 mmol). The mixture was stirred at ambient temperature for 5 minutes and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (100 mL) and water (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 25-50% EtOac:hexanes to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(trifluoromethoxy)benzyl alcohol as a colorless gum (TLC R_f = 0.24 (25% EtOAc EtOAc:hexanes)).

Step 7. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(trifluoromethoxy)benzyl alcohol (2.5 g, 6.6 mmol)) from Step 6 above and triphenylphosphine (3.46 g, 13.2 mmol) in ether (100 mL) was added carbon tetrabromide (4.35 g, 13 mmol). The mixture was stirred at ambient temperature for 14 h and the ethereal solution was decanted away from the gummy precipitate of triphenylphosphine oxide which had formed. The solvent was removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using a gradient elution of 10-15% EtOAc:hexanes to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-

(trifluoromethoxy)benzyl bromide as a colorless oil (TLC R_f = 0.55 (25% EtOAc:hexanes)).

Step 8. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(trifluoromethoxy)benzyl bromide (2.2 g, 5.0 mmol) in DMF (50 mL) was added NaCN (2.7 g, 5.5 mmol). The mixture was stirred at ambient temperature for 36 h. The solvent was removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 25% EtOAc:hexanes as eluant to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(trifluoromethoxy)phenylacetonitrile as a colorless oil (TLC R_f = 0.43 (25% EtOAc:hexanes); HPLC retention time = 11.3 min (method A)).

Step 9. 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(trifluoromethoxy)phenylacetonitrile (1.9 g, 4.3 mmol) from Step 8 above dissolved in a 2:1 mixture of acetic acid and concentrated aqueous HCl (25 mL). Loss of the Boc group occurred within the first 5 minutes to give an intermediate which had an HPLC retention time of 6.3 min (method A). The solution was then refluxed for 2 h, during which time the 6.3 min peak disappeared and a new peak at 5.9 min appeared. The solvents were removed under reduced pressure. The residue was dissolved in degassed DMF (100 mL) and the solvent was removed under reduced pressure to minimize the amount of residual acetic acid and water in the sample. The crude product, 4-(4-piperidinyloxy)-2-(trifluoromethoxy)phenylacetic acid, was dissolved in DMF (50 mL) and di-tert-butyldicarbonate (1.0 g, 4.6 mmol) and DIEA (2.3 mL, 13 mmol) were added. The solution was stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (50 mL). The organic phase was separated, washed with water (2 x 25 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(trifluoromethoxy)phenylacetic acid as a gum (HPLC retention time = 10.2 min (method A)).

Step 10. To a stirred solution of 4-(N-tert-butyloxy-carbonyl-4-piperidinyloxy)-2-(trifluoromethoxy)phenylacetic acid (1.0 g, 2.3 mmol)

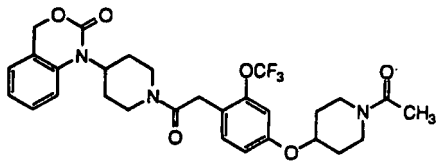
from Step 9 above and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.62 g, 2.3 mmol) from Step 4 of Example 1 in DMF (50 mL) was added HOBT (0.35 g, 2.3 mmol), EDC (1.0 g, 3.5 mmol), and DIEA (0.61 mL, 3.5 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (100 mL) and 0.25 M aqueous citric acid (75 mL). The organic phase was separated and washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (75 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using EtOAc as eluant. The product-containing fractions were evaporated under reduced pressure to give 1-(1-(2-trifluoromethoxy-4-(N-tert-butyoxycarbonyl-4-piperidinyloxy)phenyl-acetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as an amorphous solid (HPLC retention time = 11.5 min (method A); TLC R_f = 0.54 (7:3 EtOAc:hexanes).

Step 11. Into a stirred solution of 1-(1-(2-trifluoro-methoxy-4-(N-tert-butyoxycarbonyl-4-piperidinyloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (1.3 g, 2.1 mmol) from Step 10 above in EtOAc (75 mL) at 0°C was bubbled HCl gas for 15 min. The resulting suspension was stirred at 0°C for 45 min. Excess HCl was removed by bubbling argon though the mixture for 15 min. Ether (75 mL) was added and the cold suspension was filtered. The solids were washed with additional ether and dried under reduced pressure for 18 h to give the hydrochloride salt of the title compound as an amorphous white powder.
HPLC retention time = 7.4 min (method A)
TLC R_f = 0.58 (90:10:0.5 CH_2Cl_2:MeOH:NH4OH)
FAB MS: m/z = 533 ($M^+ + H$)
combustion analysis: $C_{27}H_{30}F_3N_3O_5 \cdot 1.0$ HCl, 0.87 H_2O

Calculated	C, 55.37; H, 5.63; N, 7.17
Found	C, 55.36; H, 5.57; N, 7.07

EXAMPLE 40

1-(1-(2-trifluoromethoxy-4-(1-acetyl-4-piperidinyloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



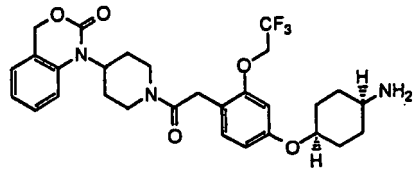
To a solution of 1-(1-(4-(4-piperidinyloxy)-2-(trifluoro-methoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.45 g, 0.77 mmol) from Example 39 in CH_2Cl_2 (50 mL) was added acetic anhydride (0.15 mL, 1.5 mmol) and DIEA (0.26 mL, 1.5 mmol). The solution was stirred at ambient temperature for 1 h and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with 0.25 M aqueous citric acid (50 mL), H_2O (25 mL), and saturated aqueous $NaHCO_3$ (75 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give the title compound as an amorphous solid.

HPLC retention time = 8.9 min (method A)
TLC R_f = 0.50 (95:5 CH_2Cl_2:MeOH)
FAB MS: m/z = 590 ($M^+ + H$)
combustion analysis: $C_{30}H_{34}F_3N_3O_6 \cdot 0.05\ CH_2Cl_2$

Calculated	C, 60.07; H, 5.58; N, 7.25
Found	C, 60.06; H, 5.42; N, 7.09

EXAMPLE 41

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-aminocyclohex-4-yloxy)phenyl-acetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of methyl 4-hydroxy-2-(2,2,2-trifluoroethoxy)phenylacetate (1.0 g, 3.9 mmol) from Step 4 of Example 32 and triphenylphosphine (1.0 g, 4.0 mmol) in THF (25 mL) at 0°C was added a solution of trans-4-(tert-butyloxycarbonyl-amino)cyclohexanol (0.86 g, 4.0 mmol) and DEAD (0.69 g, 4.0 mmol) in THF (10 mL). The mixture was stirred for 3 h at 0°C and then for 14 h at ambient temperature. The mixture was cooled to 0°C and to it was added a second equivalent of triphenylphosphine (1.0 g, 4.0 mmol) and a solution of a second equivalent of trans-4-(tert-butyloxycarbonyl-amino)cyclohexanol (0.86 g, 4.0 mmol) and DEAD (0.69 g, 4.0 mmol) in THF (5 mL). The mixture was stirred for 3 h at 0°C and then for 21 h at ambient temperature. The mixture was cooled to 0°C and to it was added a third equivalent triphenylphosphine (1.0 g, 4.0 mmol) and a of solution a third equivalent of trans-4-(tert-butyloxycarbonylamino)-cyclohexanol (0.86 g, 4.0 mmol) and DEAD (0.69 g, 4.0 mmol) in THF (5 mL). The mixture was stirred for 3 h at 0°C and then for 14 h at ambient temperature. The solvent was removed under reduced pressure. Triphenylphosphine oxide solidifed upon trituration in ether and was removed by filtration. The filtrate solvents wer removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 40% EtOAc:hexanes as eluant to give methyl 4-(cis-4-(tert-butyloxycarbonylamino)cyclohex-4-yloxy)-2-(2,2,2-trifluoroethoxy)phenylacetate as an oil (HPLC retention time = 20.1 min (method C); TLC R_f = 0.75 (1:1 EtOAc:hexanes)).

Step 2. To a solution of methyl 4-(cis-4-(tert-butyloxy-carbonylamino)cyclohex-4-yloxy)-2-(2,2,2-trifluoroethoxy)phenyl-acetate (0.20 g, 0.43 mmol) from Step 1 above in MeOH (5 mL) was added aqueous

NaOH (2 mL of a 2.7 N solution, 5.4 mmol). The mixture was heated to 70°C for 30 min and then stirred at ambinet temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was washed with water (25 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPLCusing a H_2O:CH_3CN gradient containing 0.1% TFA. The product-containing fractions were lyophilized to give 4-(cis-4-(tert-butyloxycarbonylamino)cyclohex-4-yloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetic acid as an amporphous solid (HPLC retention time = 17.4 min (method C)).

Step 3. To a stirred solution of 4-(cis-4-(tert-butyloxy-carbonylamino)cyclohex-4-yloxy)-2-(2,2,2-trifluoroethoxy)phenylacetic acid (0.15 g, 0.34 mmol) from Step 2 above and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.096 g, 0.36 mmol) from Step 4 of Example 1 in DMF (3 mL) was added HOBT (0.053 g, 0.34 mmol), EDC (0.098 g, 0.51 mmol), and DIEA (0.10 mL, 0.6 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (20 mL). The organic phase was separated and washed with H_2O (10 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-(tert-butyloxycarbonylamino)cyclohex-4-yloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as an amorphous solid (HPLC retention time = 11.9 min (method C); TLC R_f = 0.53 (95:5 CH_2Cl_2:MeOH).

Step 4. Into a stirred solution of 1-(1-(2-(2,2,2-trifluoro-ethoxy)-4-(1-(tert-butyloxycarbonylamino)cyclohex-4-yloxy)phenyl-acetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.20 g, 0.30 mmol) from Step 3 above in EtOAc (10 mL) at 0°C was bubbled HCl gas for 15 min. The resulting suspension was stirred at 0°C for 45 min. Excess HCl was removed by bubbling argon though the mixture for 15 min. Ether (25 mL) was added and the cold suspension was filtered. The solids were

washed with additional ether and dried under reduced pressure for 18 h to give the hydrochloride salt of the title compound as an amorphous white powder.

HPLC retention time = 8.2 min (method B)

TLC R_f = 0.1 (92:8:0.5 CH_2Cl_2:MeOH:NH_4OH)

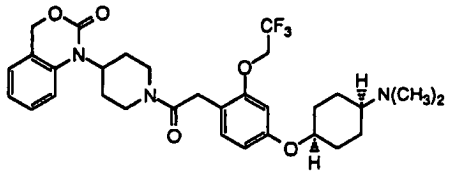
FAB MS: m/z = 562 (M^+ + H)

combustion analysis: $C_{29}H_{34}F_3N_3O_5$ •1.75 HCl, 0.2 EtOAc

Calculated	C, 55.66; H, 5.85; N, 6.53
Found	C, 55.69; H, 5.84; N, 6.52

EXAMPLE 42

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-dimethylaminocyclohex-4-yloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



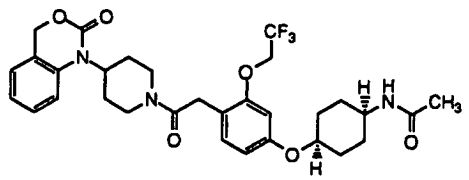
To a solution of 1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-aminocyclohex-4-yloxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.050 g, 0.09 mmol) from Example 41 in MeOH (1 mL) was added NaOAc (0.015 g, 0.18 mmol), acetic acid (0.1 mL), aqueous formaldehyde (0.045 mL of a 37% aqueous solution, 0.54 mmol), and $NaBH_3CN$ (0.027 g, 0.45 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was purified by preparative reverese phase HPLC using a H_2O:CH_3CN gradient containing 0.1% TFA. The product-containing fractions were combined and lyophilized to give the TFA salt of the title compound as an amorphous solid.

HPLC retention time = 13.1 min (method C)
TLC R_f = 0.21 (95:5:0.5 CH_2Cl_2:MeOH:NH_4OH)
FAB MS: m/z = 590 (M^+ + H)
combustion analysis: $C_{31}H_{38}F_3N_3O_5$ •1.55 TFA, 0.4 CH_3CN

Calculated	C, 53.55; H, 5.25; N, 6.08
Found	C, 53.51; H, 5.23; N, 6.12

EXAMPLE 43

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-acetylaminocyclohex-4-yloxy)-phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



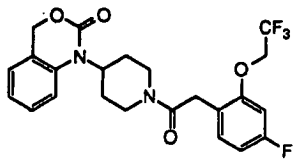
To a solution of 1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-aminocyclohex-4-yloxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.090 g, 0.15 mmol) from Example 41 in CH_2Cl_2 (4 mL) was added acetic anhydride (0.031 mL, 0.3 mmol) and DIEA (0.052 mL, 0.3 mmol). The solution was stirred at ambient temperature for 1 h and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with 0.25 M aqueous citric acid (20 mL), H_2O (10 mL), and saturated aqueous $NaHCO_3$ (20 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give the title compound as an amorphous solid.
HPLC retention time = 9.7 min (method B)
TLC R_f = 0.5 (90:10 CH_2Cl_2:MeOH)
FAB MS: m/z = 604 (M^+ + H)

combustion analysis: $C_{31}H_{36}F_3N_3O_6$ •0.6 H_2O

Calculated	C, 60.60; H, 6.10; N, 6.84
Found	C, 60.57; H, 5.85; N, 7.28

EXAMPLE 44

1-(1-(2-(2,2,2-trifluoroethoxy)-4-fluorophenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred solution of NaOH (2.0 g, 50 mmol) in water (15 mL) at 0°C was added bromine (3.0 g, 19 mmol). The solution was stirred for 10 min and a solution of 2-(2,2,2-trifluoro-ethoxy)-4-fluoroacetophenone (1.5 g, 6.4 mmol)) from Step 1 of Example 23 in dioxane (25 mL) was added dropwise over 15 min. The mixture was stirred at 0°C for 15 min, at ambient temperature for 12 h ,and then at reflux for 1.5 h. The mixture was cooled to 0°C and acidified to pH 2 by the addition of 6 N aqueous HCl. The mixture was concentrated under reduced pressure and then extracted with CH_2Cl_2 (2 x 75 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 2-(2,2,2-trifluoroethoxy)-4-fluorobenzoic acid as an amorphous solid (HPLC retention time = 7.1 min (method A)).

Step 2. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-fluorobenzoic acid (2.0 g, 8.4 mmol) from Step 1 above in THF (25 mL) at 0°C was added BH_3•THF complex (25 mL of a 1.0 M solution in THF, 25 mmol). The mixture was stirred at 0°C for 30 min and then at ambient temperature for 6 h. Aqueous NaOH (20 mL of a 4 N solution, 80 mmol)

was added and the solvents were removed under reduced pressure. The residue was partitioned between EtOAc (100 mL) and water (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 2-(2,2,2-trifluoroethoxy)-4-fluorobenzyl alcohol as an oil (HPLC retention time = 7.3 min (method A)).

Step 3. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-fluorobenzyl alcohol (1.2 g, 5.3 mmol) from Step 2 above in ether (30 mL) was added CBr_4 (3.0 g, 9.2 mmol) and triphenylphosphine (2.4 g, 9.2 mmol). The mixture was stirred at ambient temperature for 14 h. Triphenylphosphine oxide was removed by filtration and the filtrate was diluted with EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressureized silica gel column chromatography using a gradient elution of 0-5% EtOAc:hexanes to give 2-(2,2,2-trifluoro-ethoxy)-4-fluorobenzyl bromide as a colorless oil (HPLC retention time = 10.4 min (method A)).

Step 4. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-fluorobenzyl bromide (0.80 g, 2.7 mmol) from Step 3 above in DMF (14 mL) was added NaCN (0.20 g, 4.0 mmol). The mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 2-(2,2,2-trifluoroethoxy)-4-fluorophenyl-acetonitrile as an oil (HPLC retention time = 8.7 min (method A)).

Step 5. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-fluorophenylacetonitrile (0.60 g, 2.7 mmol) from Step 4 above in acetic acid (10 mL) was added 12 N aqueous HCl (5 mL). The mixture was refluxed for 4 h. The solvents were removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and water (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give 2-(2,2,2-trifluoroethoxy)-4-

fluorophenylacetic acid as an amorphous solid (HPLC retention time = 7.5 min (method A)).

Step 6. To a stirred solution of 2-(2,2,2-trifluoroethoxy)-4-fluorophenylacetic acid (0.15 g, 0.60 mmol) from Step 5 above and 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (0.17 g, 0.66 mmol) from Step 4 of Example 1 in DMF (3 mL) was added HOBT (0.11 g, 0.78 mmol), EDC (0.17 g, 0.9 mmol), and DIEA (0.16 mL, 0.9 mmol). The solution was stirred at ambient temperature for 14 h and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and 0.25 M aqueous citric acid (25 mL). The organic phase was separated and washed with H_2O (10 mL) and saturated aqueous $NaHCO_3$ (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 0-2% MeOH:CH_2Cl_2. The title compound was obtained as an amorphous solid by precipitation from MeOH.

HPLC retention time = 9.3 min (method A)

TLC R_f = 0.8 (90:10 CH_2Cl_2:MeOH)

FAB MS: m/z = 466 ($M^+ + H$)

combustion analysis: $C_{23}H_{22}F_4N_2O_4 \cdot 0.4$ MeOH, 0.04 CH_2Cl_2

Calculated C, 58.25; H, 4.94; N, 5.79

Found C, 58.21; H, 4.92; N, 5.83

EXAMPLE 45

As a specific embodiment of an oral composition, 100 mg of the compound of Example 10 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

A further embodiment is the use of any of the compounds disclosed herein for the preparation of a medicament for treating/preventing the conditions of clinical conditions for which an oxytocin receptor antagonist is indicated.

EXAMPLE 46

Rat & Human ot/avp Binding Assays

The high affinity binding of [^{3}H]oxytocin (OT) to uterine tissue and [^{3}H]arginine vasopressin (AVP) to liver (AVP-V_1 site) and kidney (AVP-V_2 site) tissue was determined using crude membrane preparations as described previously [Pettibone, D.J., et al., *J. Pharmacol. and Exper. Ther.*, 256(1): 304-308 (1991)]. Uterine tissue was taken from nonpregnant adult Sprague-Dawley rats (Taconic Farms, Germantown, NY) pretreated (18-24 h) with diethylstilbestrol propionate (DES; 300 μg/kg, i.p.). Uterine tissue (full thickness) was also taken with informed consent from nonlabor pregnant women undergoing cesarean section at 38 to 39 weeks gestation (Oregon Health Sciences Center, Portland, OR). Liver and kidney medulla samples were taken from male rats and from human surgical and early postmortem donors (National Disease Research Interchange, Philadelphia PA; Analytical Biological Services, Wilmington, DE).

Competition studies were conducted at equilibrium using 1 nM [^{3}H]OT or 0.5 nM [^{3}H]AVP in the following buffer: 50 mM Tris, 5 mM $MgCl_2$, 0.1% bovine serum albumin. Nonspecific binding was determined using 1 μM unlabeled OT or AVP in their respective assays. The binding reactions were initiated by the addition of tissue preparation and terminated by filtration using a Skatron cell harvester (model 7019, Skatron, Inc., Sterling, VA). Ki values were calculated for each compound using three to six separate IC_{50} determinations (K_i=IC_{50}/[1-c/K_d]); [Cheng, Y-C; Prusoff, W.H.; *Biochem. Pharmacol.* 22:3099 (1973)] with mean K_d values obtained from replicate (n = 3) equilibrium saturation binding assays (10 point, 100 fold concentration range): [^{3}H]OT rat uterus, 0.69 nM; human myometrium, 1.1 nM; [^{3}H]AVP: rat liver, 0.21 nM; rat kidney, 0.27 nM; human liver, 0.27 nM; human kidney, 1.4 nM. Computer analysis of the saturation assays by EBDA/LIGAND [McPherson, G.A.: Kinetic, Ebda, Ligand, Lowry: A Collection of Radioligand Binding Analysis Programs, Elsevier Science Publishers, Amsterdam (1985)] indicated that both radioligands

apparently bound to single sites in all tissues examined. The final protein concentration for the various tissues in each assay ranged from 150 to 300 μg/ml [Lowry, P.H.; Rosebrough, N.J.; Farr, A.L.; Randall, R.J.; *J. Biol. Chem.*, 193:265-275 (1951)].

IC_{50} values were determined for the [^{3}H]OT and [^{3}H]AVP binding assays by linear regression of the relation log concentration of compound vs. percent inhibition of specific binding. Data is either reported as a given percentage of inhibition at a specified concentration, or if an IC_{50} was calculated, as a nanomolar concentration.

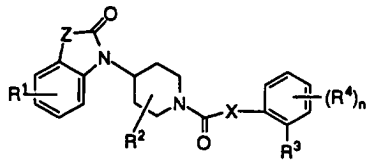
Representative compounds of the present invention were found to have IC_{50} values for oxytocin in the range of 0.1-100 nM.

The oxytocin antagonistic effect of the compounds of the present invention can be further evaluated according to the *in vitro* and/or *in vivo* functional assays described in detail in D.J. Pettibone et al., *Drug Devel. Res.* 1993, 30, 129-142.

While the foregoing specification teaches the principles of the present invention, with examples for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptions and/or modifications as come within the scope of the following claims and their equivalents.

WHAT IS CLAIMED IS:

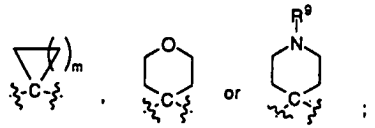
1. A compound of the formula



wherein

Z is selected from: CH_2O, where O is attached directly to the carbonyl of the ring; CH=CH; or CH_2CH_2;

X is selected from O, CH_2, CF_2,



R^1 is selected from hydrogen, halogen or C_{1-5} alkyl;

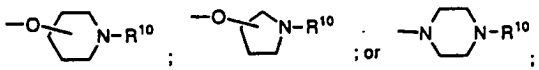
R^2 is selected from hydrogen, C_{1-5} alkyl, hydroxymethyl or $CONH_2$;

R^3 is selected from hydrogen; C_{1-5} alkoxy; mono- or polyhalogenated C_{1-5} alkoxy; substituted C_{1-5} alkoxy wherein the substituent on alkoxy is selected from carboxy, CO_2-C_{1-5} alkyl, $CONH_2$, pyridinyl or NH-R^5; unsubstituted or substituted phenyl wherein the phenyl is substituted with one to three substituents independently selected from C_{1-5} alkyl, halogen, CF_3 or CN; unsubstituted or substituted phenoxy wherein the phenoxy is substituted with one to three

substituents independently selected from C_{1-5} alkyl, halogen, CF_3 or CN; unsubstituted or substituted pyrimidinyloxy wherein the substituent is CO_2NH_2; C_{1-5} alkyl; mono- or polyhalogenated C_{1-5} alkyl; hydroxy; C_{1-5} hydroxyalkyl; mono- or polyhalogenated C_{1-5} hydroxyalkyl; C_{1-5} alkenyl; mono- or polyhalogenated C_{1-5} alkenyl; C_{1-5} alkynyl; mono- or polyhalogenated C_{1-5} alkynyl; tetrahydrofuranyloxy; tetrahydrothiophenyloxy; C_{3-7} cycloalkyloxy; or

;

R^4 is selected from hydrogen; halogen; C_{1-5} alkyl; mono- or poly-halogenated C_{1-5} alkyl; C_{1-5} alkoxy; mono- or polyhalogenated C_{1-5} alkoxy; substituted C_{1-5} alkoxy wherein the substituent on alkoxy is selected from carboxy, CO_2-C_{1-5} alkyl, $CON(R^8)_2$, $N(R^8)_2$ or morpolinyl; S-C_{1-5} alkyl; SO-C_{1-5} alkyl; SO_2-C_{1-5} alkyl; NHR^5; CN; carboxy; CO-C_{1-5} alkyl; $CON(R^8)_2$; pyridinyloxy; pyridinyloxy-N-oxide; triazolyl; tetrazolyl; morpholinyl; unsubstituted or substituted phenoxy wherein the phenoxy is substituted with one to three sub-stituents independently selected from C_{1-5} alkyl, halogen, CF_3 or CN;

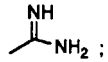


R^5 is selected from hydrogen, CO_2-C_{1-5} alkyl or $COCH_2$-Het;

each R^8 is independently selected from hydrogen or C_{1-5} alkyl;

R^9 is selected from hydrogen, C_{1-5} alkyl, C_{3-6} cycloalkyl substituted C_{1-5} alkyl, CO_2-C_{1-5} alkyl or $COCH_2$-Het;

R^{10} is selected from hydrogen, C_{1-5} alkyl, C_{3-7} cycloalkyl substituted C_{1-5} alkyl, mono or polyhalogenated C_{1-5} alkyl, mono or polyhalogenated C_{1-5} alkyloxycarbonyl, hydroxy C_{1-5} alkyl, CO_2-C_{1-5} alkyl, $CON(R^8)_2$, CO-C_{1-5} alkyl, SO_2-C_{1-5} alkyl or

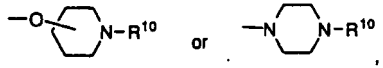


;

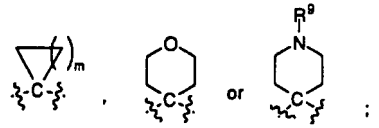
Het is selected from pyridinyl, imidazolyl and morpholinyl;

m is an integer from 1 to 5; and
n is an integer from 1 to 2;

provided that when Z is CH_2O or CH_2CH_2, and R^2 is hydrogen, C_{1-5} alkyl or $CONH_2$, and R^3 is hydrogen or C_{1-5} alkoxy, and R^4 is one or two of halogen, C_{1-5} alkoxy,



then X is selected from O, CF_2,

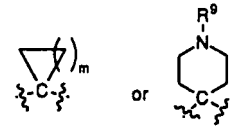


and the pharmaceutically acceptable salts thereof.

2. The compound of Claim 1, wherein

Z is selected from CH_2O or CH_2CH_2;

X is selected from O, CH_2, CF_2,



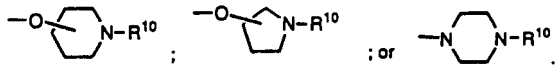
;

R^1 is selected from hydrogen or halogen;

R^2 is hydrogen;

R^3 is selected from hydrogen; C_{1-5} alkoxy; mono- or polyhalogenated C_{1-5} alkoxy; substituted C_{1-5} alkoxy wherein the substituent on alkoxy is selected from carboxy, CO_2-C_{1-5} alkyl, $CONH_2$, pyridinyl or NH-R^5; unsubstituted or substituted phenoxy wherein the phenoxy is substituted with one to three substituents independently selected from C_{1-5} alkyl, halogen, CF_3 or CN; unsubstituted or substituted pyrimidinyloxy wherein the substituent is CO_2NH_2; mono- or polyhalogenated C_{1-5} alkyl; hydroxy; tetrahydrofuranyloxy; tetrahydrothiophenyloxy; or C_{3-7} cycloalkyloxy;

R^4 is selected from hydrogen; halogen; mono- or polyhalogenated C_{1-5} alkyl; C_{1-5} alkoxy; mono- or polyhalogenated C_{1-5} alkoxy; SO_2-C_{1-5} alkyl; NHR^5; CO-C_{1-5} alkyl; pyridinyloxy; pyridinyloxy-N-oxide; triazolyl; morpholinyl;



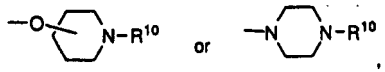
;

R^5 is selected from hydrogen or CO_2-C_{1-5} alkyl;

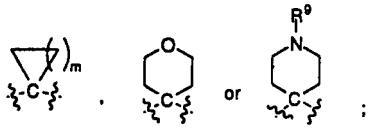
R^9 is selected from hydrogen, C_{3-6} cycloalkyl substituted C_{1-5} alkyl or $COCH_2$-Het;

Het is selected from pyridinyl or imidazolyl;

provided that when Z is CH_2O or CH_2CH_2, and R^3 is hydrogen or C_{1-5} alkoxy, and R^4 is one or two of halogen, C_{1-5} alkoxy,



then X is selected from O, CF_2,

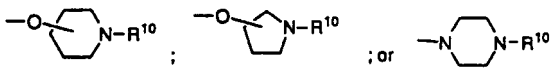


and the pharmaceutically acceptable salts thereof.

3. A compound of Claim 2 wherein R^3 is C_{1-5} alkoxy; mono- or polyhalogenated C_{1-5} alkoxy; substituted C_{1-5} alkoxy wherein the substituent on alkoxy is selected from carboxy, CO_2-C_{1-5} alkyl, $CONH_2$, pyridinyl or NH-R^5.

4. A compound of Claim 3 wherein R^3 is trifluoroethoxy.

5. A compound of Claim 2 wherein R^4 is C_{1-5} alkoxy; mono- or polyhalogenated C_{1-5} alkoxy; SO_2-C_{1-5} alkyl; NHR^5; CO-C_{1-5} alkyl; pyridinyloxy; pyridinyloxy-N-oxide; triazolyl; morpholinyl;



6. A compound of Claim 1 selected from the group consisting of:

1-(1-(4-(1-tert-butyloxycarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-acetyl-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenyl-acetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-methylsulfonyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-dimethylaminocarbonyl-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-cyclopropylmethyl-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-(2-hydroxy-1-propyl)-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-(2,2,2-trifluoroethyl)-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-(2-propyl)-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-carboxamidino-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetyl)piperidin-4-yl)-5-fluoro-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-(2-hydroxy-2-methyl)propyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(4-piperidinyloxy)-2-trifluoromethylphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(4-piperidinyloxy)-2-(2,2,3,3,3-pentafluoropropyloxy)phenyl-acetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(3-pyrrolidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-trifluoromethoxyphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(1,1,2,2-tetrafluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)phenyldifluoroacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-5-trifluoromethylphenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-3-chlorophenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-aminophenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-acetylaminophenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-methylsulfonylphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(4-morpholinyl)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-triazolyl)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(3-pyridyloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(3-(1-oxo)pyridyloxy)phenyl-acetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one;

1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one;

1-(1-(1-(4-(4-piperidinyloxy)-2-methoxyphenyl)cyclopentylcarbonyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(1-(4-methoxyphenyl)cyclopropylcarbonyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-hydroxyphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(2-(4-morpholinyl)ethoxy)phenyl-acetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(3-(4-morpholinyl)-2-hydroxy-propyloxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(3-diethylamino-2-hydroxy-propyloxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-carboxymethoxyphenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(tert-butylaminocarbonylmethoxy-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-((3,4-dihydroxypyrrolidinyl)-carbonyl-methoxyphenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-trifluoromethoxy-4-(4-piperidinyloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-trifluoromethoxy-4-(1-acetyl-4-piperidinyloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-aminocyclohex-4-yloxy)phenyl-acetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-dimethylaminocyclohex-4-yloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-acetylaminocyclohex-4-yloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-fluorophenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one,

1-(1-(2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one, and a pharmaceutically acceptable salt thereof.

7. A compound of Claim 6 selected from the group consisting of:

1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)-phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-acetyl-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenyl-acetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-cyclopropylmethyl-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-(2-hydroxy-1-propyl)-4-piperidinyloxy)-2-(2,2,2-trifluoro-ethoxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(4-(1-(2-hydroxy-2-methyl)propyl-4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(1,1,2,2-tetrafluoroethoxy)phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-acetylaminophenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(4-morpholinyl)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-triazolyl)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one;

1-(1-(4-(4-piperidinyloxy)-2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(2-(4-morpholinyl)ethoxy)phenyl-acetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(3-(4-morpholinyl)-2-hydroxy-propyloxy)-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(tert-butylaminocarbonylmethoxy-phenylacetyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-trifluoromethoxy-4-(1-acetyl-4-piperidinyloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-aminocyclohex-4-yloxy)phenyl-acetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-dimethylaminocyclohex-4-yloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-acetylaminocyclohex-4-yloxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one;

1-(1-(2-(2,2,2-trifluoroethoxy)phenylacetyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one, and a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

9. A method of eliciting an oxytocin antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

10. A method of treating preterm labor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

11. A method of stopping labor preparatory to caesarian delivery in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of

Claim 1.

12. A method of treating dysmenorrhea in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

13. A method of increasing fertility and embryonic survival in a farm animal, comprising administering to the farm animal a therapeutically effective amount of the compound of Claim 1.

14. A method for improving survival of a farm animal neonate comprising controlling timing of parturition to effect delivery of the neonate during daylight hours by administering to a farm animal which is expected to deliver the neonate within 24 hours a therapeutically effective amount of the compound of Claim 1.

15. A method of controlling the timing of estrus in a farm animal, comprising administering to the farm animal a therapeutically effective amount of the compound of Claim 1.

The Patent Office

Application No:	GB 9813103.0	**Examiner:**	Diane Davies
Claims searched:	1-15	**Date of search:**	9 September 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): C2C

Int Cl (Ed.6): C07D 413/04

Other: Online: CAS-ONLINE, EDOC, JAPIO, WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	WO 9622775 A	(Merck & Co. Inc.) Whole document: compounds of formula I where n=1 which are oxytocin receptor antagonists.	At least claim 1
X	WO 9519773 A	(Merck & Co. Inc.) Whole document: compounds of formula I which are oxytocin receptor antagonists	At least claim 1
X	WO 9502405 A	(Merck & Co. Inc.) Whole document: compounds of formula I where m=1 and W is CH_2 which are oxytocin receptor antagonists.	At least claim 1

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.